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Late-Stage C-H & N-H Functionalisation of Benzodiazepines and Other Privileged Scaffolds



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Supervisor: Prof. John Spencer

Submitted to the University of Sussex in part fulfilment of the
requirements of the degree of Doctor of Philosophy

April 2018

Declaration

I hereby declare that all work described in this thesis was carried out at the University of Sussex under the supervision of Professor John Spencer from October 2014 to March 2018. The work presented in this thesis is my own unless otherwise stated. This thesis conforms to an ‘article format.’ Following from the general Introduction in Chapter 1, Chapters 2, 3, 5 and 6 consist of articles written and published in peer-reviewed journals. Chapter 4 contains unpublished content and Chapter 7 contains the conclusions and suggestions for future directions.

Chapter 2 is published in *Advanced Synthesis and Catalysis* as:

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The author contributions are as follows: The research topic was conceptualised by Raysa Khan and John Spencer. Raysa Khan was responsible for conducting all the chemistry experimental, data collection, data analysis and the preparation of the manuscript. John Spencer provided feedback on study design, data interpretation and corrections to the manuscript. Simon J. Coles and Graham J. Tizzard were responsible for X-ray crystallography. Iain J. Day was responsible for helping with NMR studies. Paul D. Kemmitt and Robert Felix were industrial supervisors.

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on which this scale-up work was based, and provided some input into experimental design. John Spencer and Graham Marsh provided feedback on study design and corrections to the manuscript. Paul D. Kemmitt and Robert Felix were industrial supervisors.

I hereby declare that this thesis has not been and will not be, submitted in whole or in part for the award of any other degree.

Raysa Khan

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Abstract

This thesis focuses on developing efficient, atom-economic synthesis routes for functionalised 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one libraries. 1,4-Benzodiazepines (BZDs) are often referred to as “privileged scaffolds” due to their important biological activities; therefore, finding new efficient methods for synthesising such analogues is highly desirable in pharmaceutical and medicinal research.

Chapter 1 introduces the project detailing the biological importance and applications of BZDs. The classical synthetic routes towards BZDs and some of the limitations for efficient and rapid BZD-based library synthesis, followed by the aims of the project.

Chapter 2 presents a late-stage C-H activation method for synthesising ortho-arylated 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, including a library of over twenty novel analogues. The microwave-mediated palladium catalysed arylation method is also applicable to nordazepam (7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), the active metabolite of diazepam. Further diversification of the compounds is achieved by *N*-alkylation and/or H/D exchange, which affords elaborated pharmaceuticals.

Chapter 3 describes an alternative catalytic visible light-mediated photoredox method for ortho-arylated 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones. The protocol uses aryldiazonium salts in refluxing methanol and showcases an interesting phenomenon known as the “nuisance effect” with 2- or 4-fluorobenzenediazonium salts. It results in both fluoroaryl and methoxyaryl- products, the latter result from a nucleophilic aromatic substitution (S_NAr) on the fluorobenzenediazonium salt (nuisance effect). The results from biological tests of the benzodiazepine libraries against GABA_A receptors indicated that the C-7 substituent is vital for activities in GABA and only the 7-chloro-benzodiazepines show any reasonable activities, although ortho arylation is detrimental to bioactivity. A computational DFT analysis of the reaction mechanism from our collaborators is also discussed in the Chapter.

Chapter 4 contains a brief overview of C-H functionalisation protocols. Moreover, in this Chapter, the photoredox C-H activation method combined with the nuisance effect are extended to other privileged scaffolds. This Chapter describes the synthesis of small libraries of 2-phenylpyridines and 1-phenyl-2-pyrrolidinones. The nuisance effect proves to be effective in creating small arrays of compounds from a single reaction and in X-ray screening arrays for biological testing. A number of 1-phenyl-2-pyrrolidinone analogues display promising biological activities towards NUDT7, a peroxisomal coenzyme A diphosphatase of current interest.

Chapter 5 focuses on the synthesis of a series of *N*1-arylated 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones. The *N*-arylation occurs in one-step using a single 1,4-benzodiazepine precursor with unsymmetrical diaryliodonium salts in aqueous ammonia as a base.

Chapter 6 reports the scale-up synthesis of 6-(1*H*-indol-4-yl)-8-methoxy-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-4-acetic acid methyl ester, **TC-AC-28**. This BZD derivative is a highly selective bromo and extra terminal (BET) bromodomain inhibitor and a useful epigenetic tool compound. The near gram-scale, seven-step synthesis of this key chemical probe compound enabled it to be available for researchers through Tocris, one of our industry sponsors, and where I spent 3 months as part of my CASE award.

Chapter 7 concludes the thesis and concentrates on future directions.

List of abbreviations

Å	angstrom
Ac	acetate
ACOT	acyl-CoA thioesterase
AcOH	acetic acid
ADME-Tox	Absorption, distribution, metabolism, elimination-toxicity
Ar	aryl
Asp	aspartic acid
atm	atmosphere
BDE	bond dissociation energies
BET	bromodomain and extraterminal domain
Boc	tert-butyloxycarbonyl
br	broad
BRD	Bromodomain
BZD	benzodiazepine
Cbz	carboxybenzyl
CCK	cholecystokinin
CNS	central nervous system
CoA	coenzyme A
CO ₃	carbonate
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublets of doublets
DFT	Density functional theory
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid

DG	directing group
ET	Endothelin
EtOAc	ethyl acetate
ESI	electrospray ionisation
eq	equivalent
FG	functional group
Fmoc	fluorenylmethyloxycarbonyl chloride
g	gram
GABA	gamma-aminobutyric acid
GIT	gastrointestinal tract
GP	glycoprotein
GPCR	G-protein coupled receptors
HAT	histone acetyl transferase
HDAC	histone deacetylase
HDACi	HDAC inhibitor
HDM2	human double minute 2
HIV	human immunodeficiency virus
HMP	4-hydroxymethylphenoxyacetic acid
HRMS	high resolution mass spectra
Hz	hertz
KOR	kappa opioid receptors
LC-MS	liquid chromatography – mass spectrometry
LSF	late stage functionalization
m	multiplet
MCR	multicomponent reaction
MeOH	methanol
mg	milligram
min	minute
mL	millilitre
mmol	milli-mole
MW	Microwave
MHz	megahertz
NMR	nuclear magnetic resonance
NK	Neurokinin

nM	nanomolar
NMC	midline carcinoma
NMP	N-methylpyrrolidinone
NUT	nuclear protein in testis
o/n	overnight
p53	protein 53 DK
PanNET	pancreatic neuroendocrine tumours
PCAF	p300/CBP-associated factor
PKAN	pantothenate kinase-associated neurodegeneration
PNS	peripheral nervous system
PPI	Protein-protein interaction
ppm	parts per million
pt	pseudo triplet
PTH	parathyroid hormone
PTM	post-translational modification
q	quartet
Rh	rhodium
RMSD	root mean square deviation
rt	room temperature
s	singlet
SAHA	suberoylanilide hydroxamic acid
SAR	structure activity relationship
sirtuins	silent information regulator related proteins
S _N Ar	nucleophilic aromatic substitution
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
tR	retention times
Ugi-4CR	Ugi four-component reaction
W	watt
w/w	weight/weight
μL	microlitre
μg	microgram

μM

micromolar

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Chapter 1

1.1 Benzodiazepines

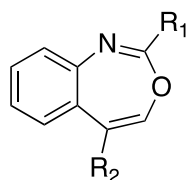
Benzodiazepines (BZDs) are most famous for their successful and wide use in treating disorders such as anxiety, depression and insomnia since the 1960s.¹ Shortly after their discovery, BZDs largely replaced other anxiolytics and sedatives in the market, due to their superior pharmacological and toxicological evaluation. BZD usage reached its peak during 1975-1980. In 1979 *ca.* 31 million prescriptions were issued for benzodiazepines in the U.K. alone and they are widely used as central nervous system (CNS) agents even today.² Being clinically effective and popular for their psychotropic effects, BZDs were hailed as wonder drugs and the Rolling Stones even released a hit single in 1960s about Valium, a potent BZD-anxiolytic, calling it “*Mother’s Little Helper*”, describing how it helped women to go through their busy days. However, just like *every rose has its thorn*, concerns soon appeared for the side effects and dependence developed among patients for BZDs.^{3–5} During 1990, manufacturers of BZD drugs faced the largest *class-action lawsuit* by 14,000 patients and 1,800 law firms in the U.K., for allegedly withholding potential dependence information on BZDs from medical staff. Moreover, in 2013, more than 7000 people died of BZD-overdose.⁶ The slightly controversial status of BZDs also presents new opportunities and challenges for chemists in developing improved BZD analogues without the side effects. Despite, their long-standing clinical use as anxiolytics, what makes BZDs attractive in medicinal research is their ability to bind not only to the receptors in the CNS but also to a diverse array of other protein and enzyme receptors by modifying the substituents on the BZD core. This class of compounds are therefore often referred to be “privileged” in drug discovery, i.e., they have the capacity to interact with multiple proteins and alter the course of diseases.⁷ The therapeutic potential of compounds containing BZD moieties has captured the interest of synthetic chemists in finding new protocols for developing a range of functionalised BZDs. A major part of

this project indeed is concerned with developing effective routes for synthesising a range of novel 1,4-benzodiazepin-2-one analogues.

This chapter entails the story of the accidental discovery of BZD derivatives as CNS acting agents and how they work, the subsequent development of a range of BZD analogues targeting numerous enzymes and proteins, various routes for synthesising BZDs and finally the aims of the project.

1.2 The discovery

BZDs are bicyclic compounds consisting of a benzene nucleus attached to a seven-membered ring containing two nitrogen atoms.⁸ Leo Sternbach first synthesised BZDs during the 1950s when Roche laboratories initiated a project for making new tranquilisers, since this class of therapeutics were rising in clinical demands at the time. Initially, Sternbach attempted to synthesise a series of novel benzheptoxdiazines for the project, as these were a relatively unexplored but chemically interesting group of compounds.

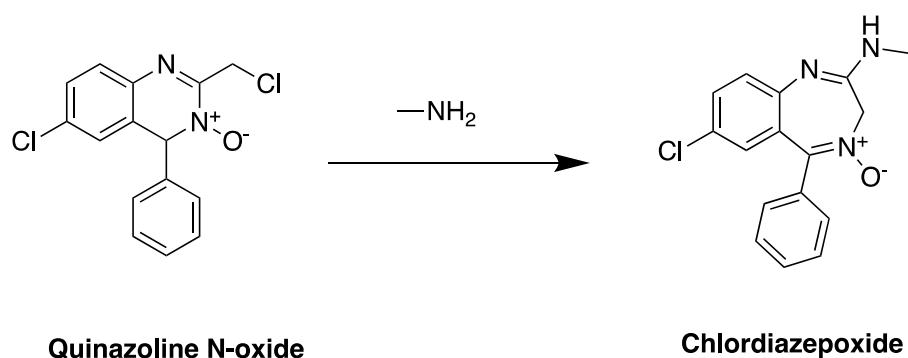


Benzheptoxdiazine

Figure 1.1: Structure of a benzheptoxdiazine

However, the project was soon abandoned as none of the synthesised compounds displayed any interesting biological properties and studies also revealed that the compounds were not actually benzheptoxdiazines but were, in fact, quinazoline 3-oxides.⁹ About two years later in 1957, during a lab clean up, Sternbach's co-worker, Earl Reeder, found two untested samples - a crystalline base and its hydrochloride salt. The compound was synthesised by treating quinazoline N-oxide with methylamine.¹⁰ Although these two compounds were not tested initially due to lack of interest, they

decided to submit the samples for pharmacological testing, anticipating a negative result and expecting to conclude the work on quinazoline 3-oxide with this result. Surprisingly, the compound showed unusually interesting properties in the initial screenings for sedative and tranquilliser effects. Further studies showed that the compound was actually a benzodiazepine derivative, the product of an unusual novel ring enlargement of the quinazoline derivative as shown in Scheme 1.1.



Scheme 1.1 Formation of a benzodiazepine by ring enlargement of a quinazoline – oxide

This compound, with the generic name chlordiazepoxide (7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide), displayed higher anticonvulsant activities than any other marketed drugs at the time such as chlorpromazine and phenobarbital (Figure 1.2).^{9,11} Within a very short time a patent was approved for 2-amino-1,4-benzodiazepine compounds. Chlordiazepoxide was subsequently introduced in the market within a record time during 1960, under the trade name Librium®, due to its promising clinical and toxicological evaluation.¹²

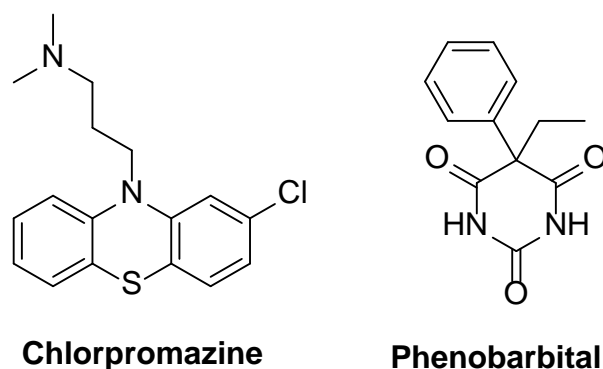


Figure 1.2: Structures of chlorpromazine and phenobarbital

Owing to their valuable clinical properties, a vast number of benzodiazepines were synthesised and their pharmacology was studied extensively.¹³ Structure-activity-relationship (SAR) investigations revealed that the 5-phenyl-1,4-benzodiazepine ring system was a key feature for biological activity (Figure 1.3). Another significant substituent for the biological property was found to be R_2 at C-7. Electron withdrawing groups at C-7 potentiated biological activity whereas electron-donating groups at the same position had the opposite effect. A substituent on the ortho-position of the phenyl ring (R_3) was associated with increased activity, on the other hand, a substituent in the para-position (R_4) decreased it significantly. An alkyl group at the N-1 position also produced a positive effect on the activity.¹⁴

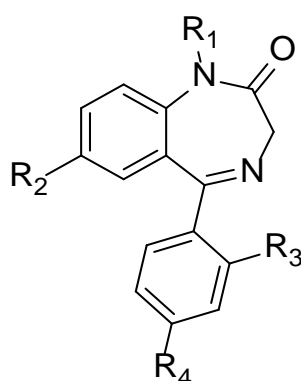


Figure 1.3: 5-Phenyl-1,4-benzodiazepin-2-one

Extensive clinical and experimental data established that BZDs possessed superior efficacy than other depressants such as barbiturates and propanediol carbamates.

Benzodiazepines have rapid onset of action, low toxicity and effective therapeutic actions.¹⁵ Additionally, they display weaker hepatic enzyme inducing properties and therefore cause fewer drug-drug interaction by this mechanism. BZDs also have a larger difference between the “effective” dose and the “lethal” dose compared to other anxiolytics. Due to this increased safety of BZDs in the context of overdose, along with other pharmacological and toxicological advantages, BZDs largely replaced other types of sedatives and hypnotics in the market.¹⁶ Subsequently, a host of 1,4-benzodiazepine compounds became available for clinical use, most of which were anxiolytics, some were hypnotics and some were even used in the treatment of epilepsy. In other words, BZDs started dominating the market for treating insomnia, muscle spasm, anxiety, depression, stress and epilepsy.

One of the most potent and most well-known benzodiazepines is diazepam (Valium®), other therapeutics include nitrazepam (Mogadon®), oxazepam (Serax®), medazepam (Nobrium®), flurazepam (Dalmane®), chlorazepate (Tranxilium®), bromazepam (Lexotan®), alprazolam (Xanax®), flunitrazepam (Rohypnol®) and clobazam (Frisium®), clonazepam (Klonopin®) and lorazepam (Ativan®).¹⁷ The structures of some clinically used BZDs are shown in Figure 1.4.

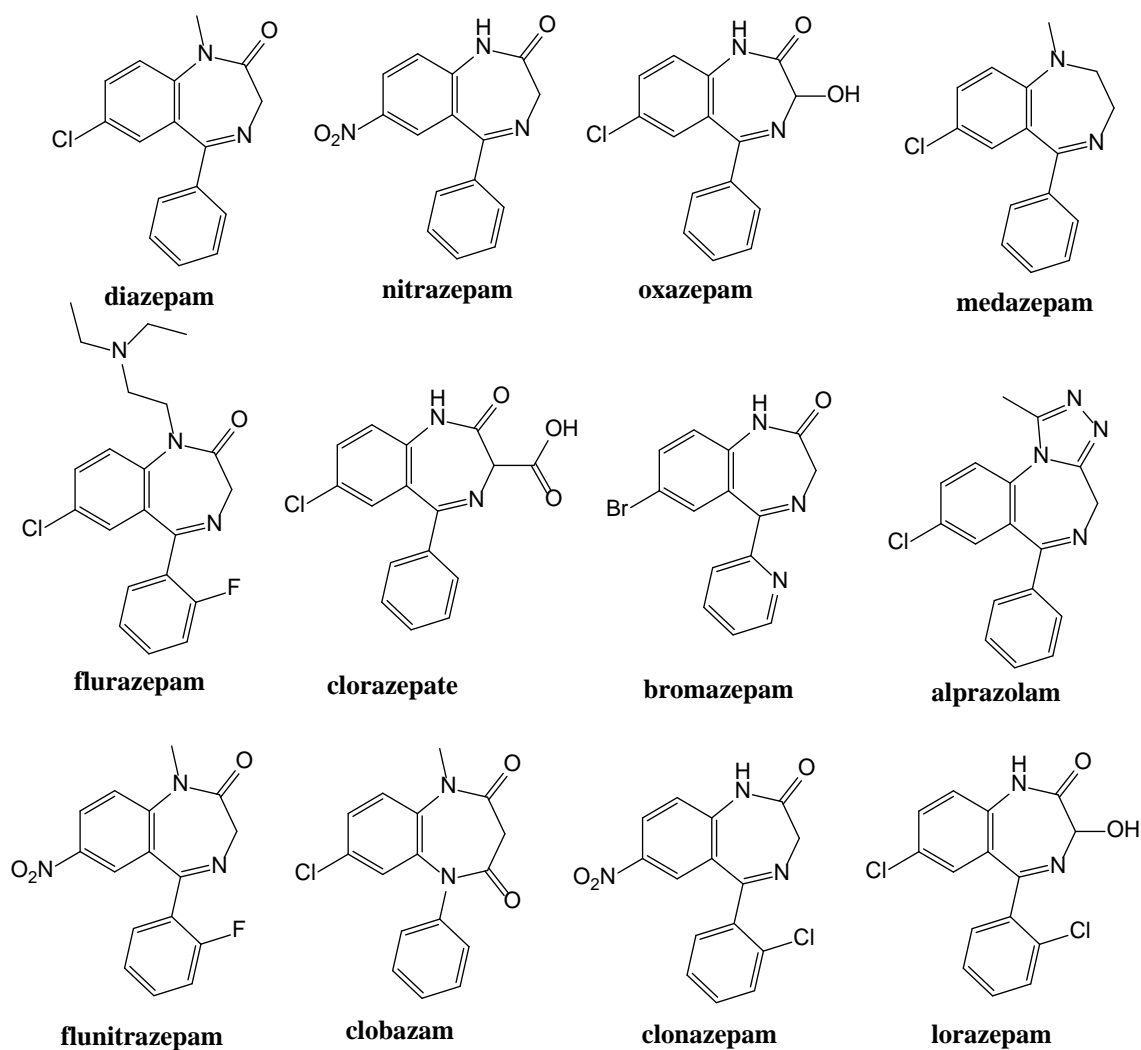


Figure 1.4: Structures of clinically available benzodiazepines

However, during the 1980s the side effects of BZDs and dependence developed for this class of drugs became concerning. The over enthusiastic prescription of BZDs was an alarming fact as well.^{4,5,18} Over the years concerns over benzodiazepine use have been associated with side effects such as drowsiness and ataxia, over-prescription, misuse of the drug, and developing dependence and withdrawal symptoms when discontinued.¹⁹ In the past years benzodiazepines have been reported to be the second most misused therapeutic and the second most frequently used drug for suicide attempts, surpassed only by the opioids.^{18,20} Due to these concerns, significant effort is still ongoing to develop improved BZD-based drugs without the side effects.

1.3 Pharmacology

There have been extensive studies in understanding the use, biochemical effects and actions of the BZDs, and how and where they bind to produce the psychotropic effects. Each BZD derivative differs from the others based on their chemical structure and pharmacokinetic properties, however, in general all BZDs share a common mechanism of action in producing the clinical effects.¹⁴ All BZDs are involved in enhancing the actions of gamma-aminobutyric acid (GABA), a widely distributed inhibitory neurotransmitter (Figure 1.5) in the CNS. GABA acts by binding to specific receptors known as GABA-receptors, in the plasma membrane during the synaptic neuronal process. This opens up ion channels on the neuron allowing negatively charged chloride ions to enter the neuron. This leads to an overall negative change in the transmembrane potential which makes the cell less responsive to other neurotransmitters resulting in reduced excitation.²¹

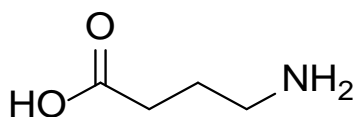


Figure 1.5: gamma-aminobutyric acid

There are at least two classes of known GABA receptors: GABA_A are ionotropic receptors that contain a central ligand-gated ionophore and GABA_B are guanine nucleotide-binding (G-protein) protein-coupled complexes, which are metabotropic receptors meaning they are connected to the ion channel on the plasma membrane through G proteins. GABA_A complex is the key medium for performing inhibitory control in the CNS. There are five specific binding domains for GABA, barbiturates, picrotoxin, anaesthetics and benzodiazepines on the GABA_A receptor. The GABA-binding site is located near/on the ionophore-channel and is candidly responsible for the opening of the Cl⁻ channel.²²

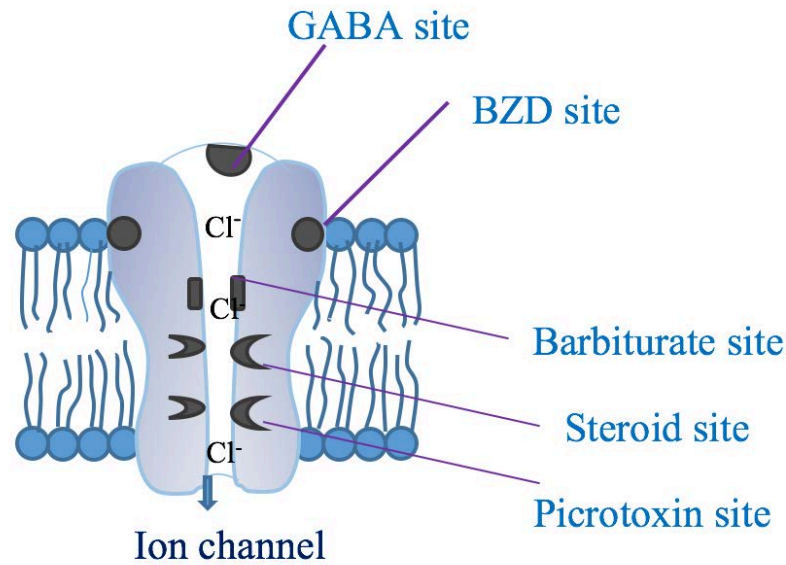


Figure 1.6: the GABA_A receptor and the binding domains

Drugs such as BZDs and barbiturates are known as *positive allosteric modulators* for GABA_A receptor – once they bind to their binding sites, this causes a conformational change in GABA_A receptor allowing GABA to bind and this in turn alters the ion channel allowing more chloride ion flow into the cell by increasing the frequency or duration of the channel opening. This leads to hyperpolarisation of the neuron, thus, decreasing the possibility of an action potential and inducing sedative effects. However, this effect is only observed when GABA or a GABA agonist is also present. The *positive allosteric modulators* have no effects on their own.²³

The composition of GABA_A receptors varies from region to region in the CNS and affects their affinity to bind to GABA and drugs such as BZDs, barbiturates and neuro active steroids.^{24–26} Each GABA_A receptor typically consists of 5 subunits. Over the years, 19 different GABA_A receptor subunits have been identified; these include six α , three β , three γ , π , δ and three ϵ , θ , ρ . The most common types of GABA_A receptors consist of two α , two β and one γ subunits.²⁷ The benzodiazepine binding sites are known to form in the interface between α and γ subunits. BZDs only display binding affinity towards α subunits containing histidine (e.g. α_1 , α_2 , α_3 and α_5 subunits) but, do not show any affinity when they contain arginine (e.g., α_4 , α_6 subunits).²⁸ Moreover, the affinities of different BZDs

vary towards the binding sites consisting of different subunits. For instance, BZDs that show higher affinity for α_1 subunit tend to produce sedative effects, whereas BZDs with higher affinity for the receptors containing α_2 mediate anti-anxiety effects.²⁹ Rational drug design to target specific receptor subtypes has been possible utilising such pharmacology of BZDs.³⁰

BZDs are typically administered orally but they can also be administered intramuscularly, intravenously or rectally. BZDs and their metabolites are highly lipophilic leading to rapid absorption and distribution. The onset and duration of action of any BZD are influenced by the distribution and absorption rates.³¹ The absorption and distribution rates are largely depended on the chemical characteristic of the BZD and the binding affinity towards the varying GABA_A receptors. BZDs can be categorised by their biochemical half-life values: long-acting BZDs have half-life values of longer than 24 hours and often have active metabolites; BZDs with half-life values ranging from 5 to 24 hours are described as intermediate or short-acting BZDs and these often do not have any active metabolites; ultrashort-acting BZDs have half-lives of below 5 hours. Notably, half-lives of the drugs may overlap amongst the groups of BZDs and vary among individuals.³²

BZDs such as chlordiazepoxide, diazepam, clobazam and flurazepam are often classified as long-acting BZD and have active metabolites with much longer half-lives than the parent molecules. Demethylated-diazepam, nordazepam, is a common metabolite of this class of BZDs and has a half-life exceeding 200 hours. The advantages of long-acting drugs include their ability to produce an effect for anxiety and insomnia by a single bedtime dosage, however, it can also have undesired drowsiness and poor coordination throughout the day. Therefore, drug accumulation is a common occurrence in multiple doses of long-acting BZDs. Rare side effects of these drugs include nausea, dizziness, confusion and nightmares. The clearance of these drugs is affected by old age and liver diseases.³³

Intermediate to short-life BZDs include lorazepam, alprazolam, oxazepam and bromazepam. Due to shorter half-lives and generally lack of active metabolites, drug accumulation during longer therapy is not prominent. Drug-accumulation is essentially non-existent in multiple dose therapy of ultrashort acting BZDs such as midazolam and triazolam. Short and ultrashort BZDs are used for hypnotic effects where residual daytime

effects need to be avoided. This type of BZDs can also be used for their amnesia effect before minor and major surgeries, however, blackout is also one of the considerable side effect caused by these drugs.³⁴ Although pharmacokinetic classification is valuable in understanding the pharmacological actions of the BZDs, it is not comprehensive to explain all of their clinical actions.

Most benzodiazepines are oxidatively metabolized by the P450 enzyme system and excreted in urine. Being the substrates of CYP3A4 enzyme, some BZDs can interfere with therapeutics that are inhibitor or inducer of this enzyme. Especially, the long-acting BZDs with active metabolites can significantly decrease the rate of clearance for these therapeutics.³⁵

1.4 1,4-Benzodiazepine as a privileged scaffold

In 1988 Evans *et al.*, first used the term “privileged scaffold” for the 1,4-benzodiazepine core structure to describe their ability to interact with a diverse array of protein receptors and therefore able to be utilised in treating different types of diseases.³⁶ Therefore, being privileged, BZD derivatives are not only active on the BZD receptors in the CNS, they display biological activities towards a wide range of enzymes and protein receptors. Over the years, many other properties have been attributed to this class of compounds. Some of these include anti-viral, anti-inflammatory, anti-tumour, anti-HIV and anti-microbial properties.³⁷

Evans *et al.*, reported that diazepam-like BZD drugs could be modified to develop cholecystokinin (CCK)-1 antagonists with increased activity than that of asperlicin, a natural compound that was already known to exhibit activity on CCK receptors.³⁸ CCK is a class of peptide hormone that is widely found in the gastrointestinal tract (GIT) and in the brain, and is responsible for regulating various functions in the GIT and the nervous system. In the GIT, CCK is responsible for pancreatic secretion, regulating gastric, bowel motility and gallbladder contraction and thereby plays vital roles in GI disorders such as pancreatitis, gastric reflux, gastro-paresis and dyspepsia. CCK is associated with anxiety, nociception, memory, learning and satiation in the CNS.³⁹⁻⁴¹ CCK performs its roles by binding to G-protein coupled CCK receptors. There are two types of CCK receptors:

CCK-1 (previously known as CCK A) and CCK-2 (previously known as CCK B). CCK-1 shows high binding affinity towards sulfated CCK, whereas, CCK-2 displays equal binding affinity towards gastrin and CCK hormones.⁴²

Asperlicin's (the original compound with a binding affinity towards CCK-1) structure was used as a guide to developing the BZD based antagonist, devazepide, with much higher binding affinity than asperlicin.⁷ Devazepide was developed by installing the 5-phenyl-1,4-benzodiazepin-2-one ring in the left part and 3-hydroxyindoline unit in the right part of asperlicin (Figure 1.7). Devazepide became the first specific non-peptide BZD antagonist with high binding affinity (IC_{50} of 0.8 nM) towards CCK-1.

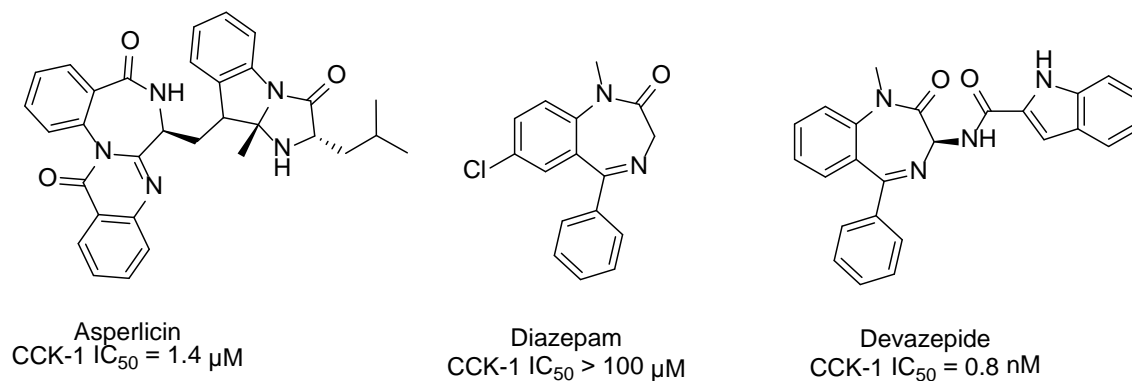


Figure 1.7: The development of a CCK-1 antagonist

Modification of privileged scaffolds became a useful approach in medicinal chemistry to develop various receptor agonists and antagonists. As a result, a vast number of 1,4-benzodiazepine analogues were then developed as gastrin/CCK (1 and 2) receptor antagonists.^{40,43–47} Figure 1.8 shows a few selected structures of such CCK receptor antagonists.

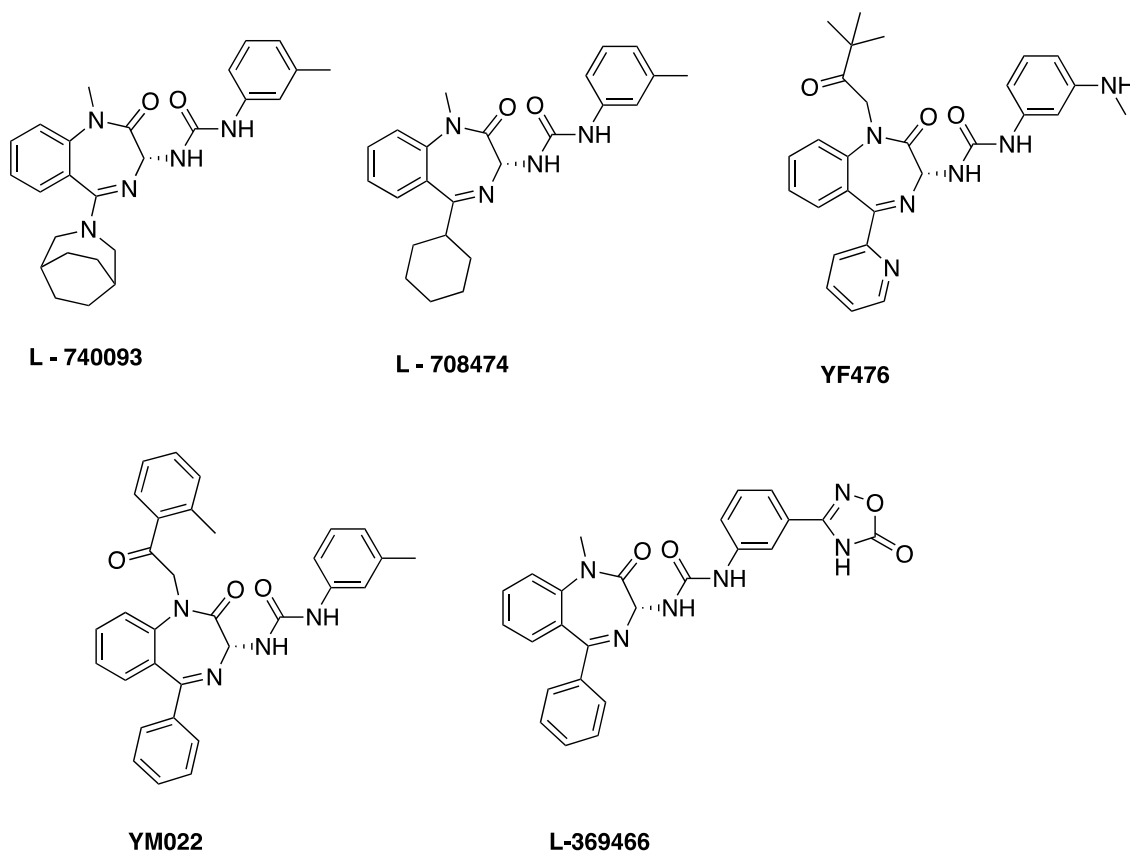
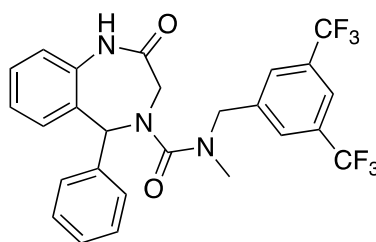


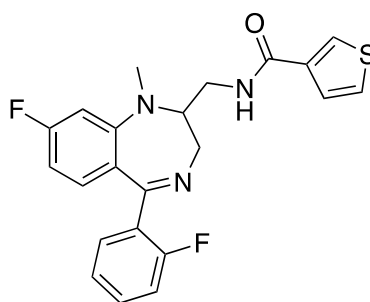
Figure 1.8: 1,4-benzodiazepine CCK receptor antagonists

An extensive number of 1,4-benzodiazepine ligands have been synthesised and used for various applications in many other G-protein coupled receptors (GPCRs). Some of these developments are outlined below.

Neurokinin (NK-1) receptors are expressed both in the CNS and peripheral nervous system (PNS) and are implicated in inflammation, contraction of muscles, stress signals and pain. This class of receptors share intriguing structural similarities with CCK receptors. Both classes bind to their non-peptide ligands in a similar pattern between the transmembrane helices. Therefore, following the successful development of BZD based non-peptide antagonists for CCK-receptors, a number of BZD containing antagonists were reported for NK-1 receptors possessing analgesic and anti-inflammatory properties.^{48,49}

**1.1***Figure 1.9: Structure of an NK1 receptor antagonist 1.1: K_i 10 nM*

Another member of the GPCR family includes the kappa opioid receptors (KORs), a highly distributed type of receptors in the areas of the brain involved in cognitive function, motivation and emotion. Tifluadom is a BZD analogue that has uses in analgesia and in for the treatment of visceral pain due to its activity in the KORs as a κ -selective opioid agonist.⁵⁰

**Tifluadom***Figure 1.10: Structure of a κ -selective opioid agonist*

BZD derivatives have been developed as antagonists of platelet-activating factor (PAF), a phospholipid mediator of platelet aggregation, inflammation and many leukocyte functions.⁵¹ Additionally, glycoprotein (GP) IIb-IIIa is a key receptor for mediating platelet aggregation.^{52,53} Platelets are activated by various agonists that give rise to the binding of fibrinogen and other adhesive ligands to platelet GPIIb-IIIa. As uncontrolled aggregation can result in thrombotic disorders, there has been significant effort towards developing therapeutics to control platelet aggregation by inhibiting the binding of platelet GPIIb-IIIa to fibrinogen.⁵⁴ The binding occurs via the interaction of activated platelet GPIIb-IIIa and the RGD sequence, the key structural motif of fibrinogen that is found in the II' Arg-Gly-Asp β -turn conformation. The 1,4-benzodiazepine scaffold was

functionalised to develop RGD sequence mimetics and resulted in numerous potent antagonist of platelet GPIIb-IIIa.^{55,56}

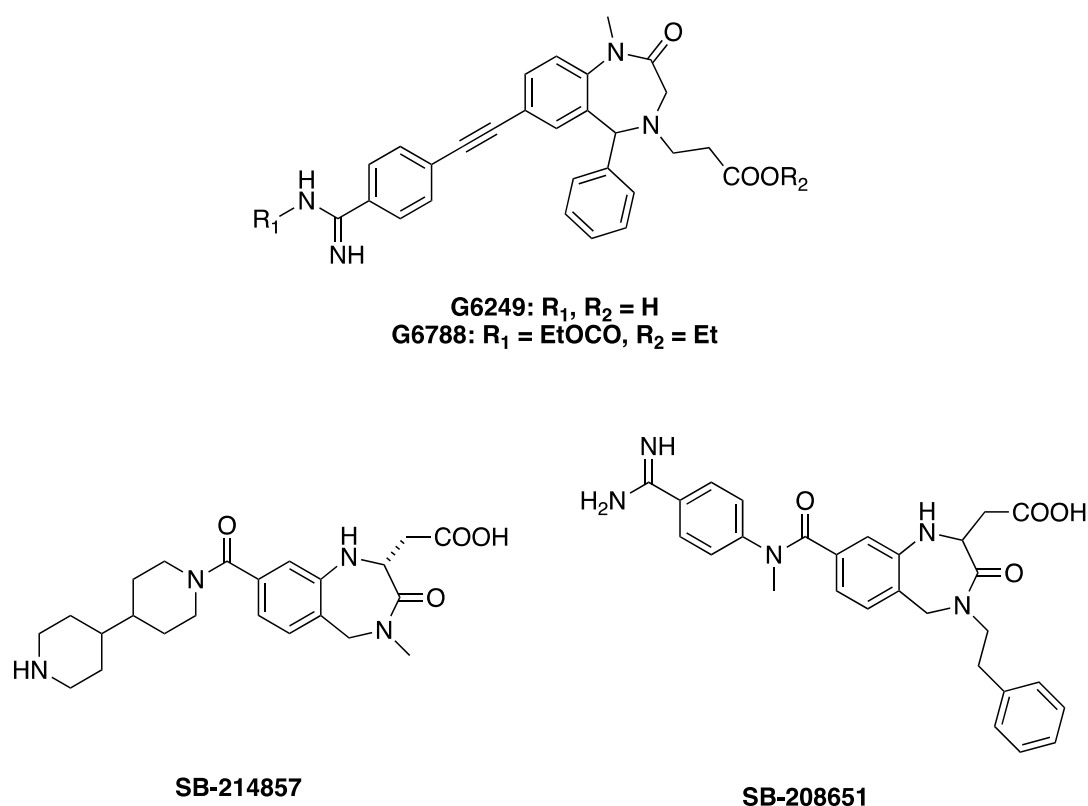


Figure 1.11: Structures of selective glycoprotein GPIIb-IIIa antagonists

Above are the structures of a few BZD based potent inhibitors of platelet aggregation. G6788 is synthesised by inserting aspartate and argininy side chains on the 1,4-benzodiazepine scaffold and G6249 (IC_{50} 120 nM) is the active metabolite of the double prodrug G6788. A glycine side chain on the right part and another extension on the left side of the BZD nucleus yielded inhibitor SB-208651 (IC_{50} 65 nM). The activity was further improved in SB214857 (Ilotrafiban) by replacing the benzamide group with less basic piperidine group (IC_{50} 28 nM).^{57,58}

Endothelin (ET) was identified as a potent vasoconstrictor in 1988.⁵⁹ The receptors for this class of protein, ET_A and ET_B are distributed in the smooth muscle cells of the blood vessel of kidney, liver, heart, spleen, the smooth muscle of the lungs and parts of the brain. They play vital roles in strong vasoconstriction, fibrosis and cell reproduction.^{60,61}

ET is implicated in the physiological disorder of kidney, cardiovascular such as renal failure, heart attack, hypertension and atherosclerosis.⁶⁰⁻⁶² It is proposed that a reasonable approach to developing new treatments and drugs to prevent these disorders could be by targeting the ET receptors. Accordingly, in 2004, a potent class of ET receptor antagonists were reported based on the 1,4-benzodiazepin-2-one subunit. One of the most potent antagonists, **1.2** is presented in Figure 1.12. **1.2** displays over 30 times higher binding affinity towards ET_A (IC₅₀ 2.5 ± 0.4 nM) than ET_B (IC₅₀ 83.6 ± 8.8 nM).⁶³

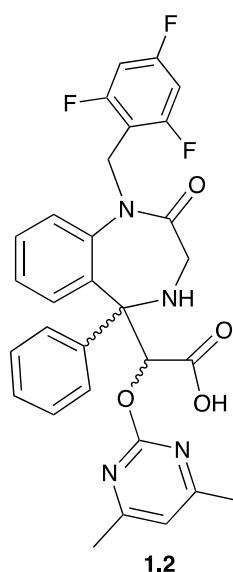


Figure 1.12: Structure of an endothelin antagonist

Bradykinin is a linear peptide hormone implicated in bronchial and vascular smooth muscle contraction, vasodilation and causes blood pressure to fall. This peptide performs its functions through two types of receptors, namely B₁ and B₂. Bradykinin induces acute pain after tissue injury by serving as the agonist on the B₁ and B₂ receptors.⁶⁴ Considerable effort has been carried out in order to develop antagonists of these receptors due to the physiological disorders caused by bradykinin. Spectroscopic analysis and computational studies suggested that the binding of bradykinin to the B₂ occurs through the adoption of bradykinin C-terminal β-turn conformation comprising residues Ser⁶-Pro⁷-Phe⁸-Arg⁹. The binding affinity of one of the most potent antagonists of the B₂ receptors, HOE 140 (H-D-Arg⁰-Arg¹-Pro²-Hyp³-Gly⁴-Thi⁵-Ser⁶-D-Tic⁷-Oic⁸-Arg⁹-OH) also depended on its ability to adopt the β-turn conformation. Since the BZD scaffold was already known to

be a good β -turn peptidomimetic, chemists developed a number of B₁ and B₂ receptors antagonists based on the BZD nucleus.^{65–67}

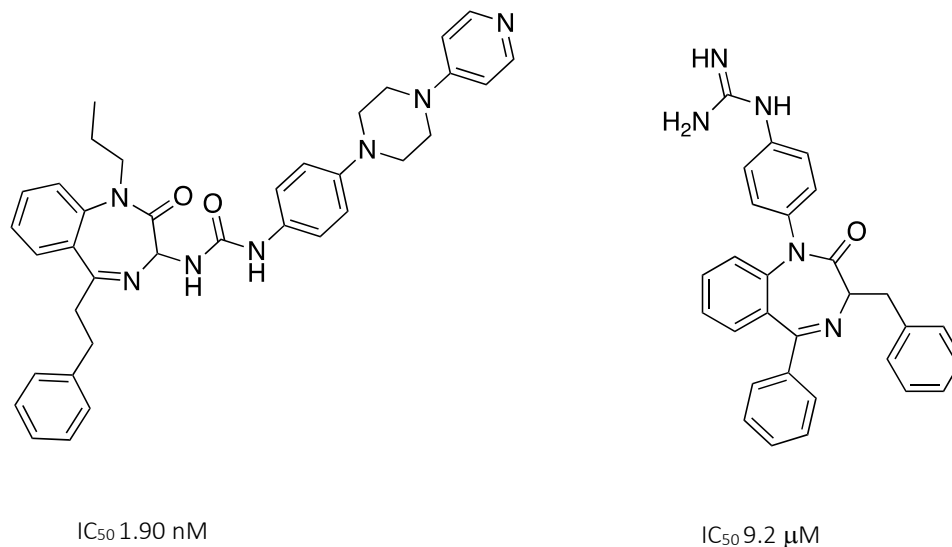


Figure 1.13: Structures of selected bradykinin antagonists

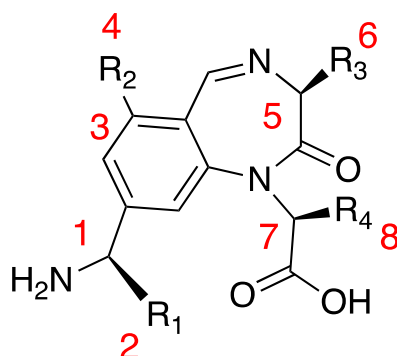
BZD derivatives have been reported as oxytocin receptor antagonists. Oxytocin is a peptide hormone that plays vital role in premature birth and labour.^{52,53,68} Other applications of BZD core based analogues in GPCRCs include vitronectin receptor antagonists,⁶⁹ fibrinogen receptor antagonist⁷⁰ anti arrhythmic agents,⁷¹ and calcitonin gene related peptide receptor antagonists.⁷²

1.4.1 Benzodiazepines as PPI inhibitors

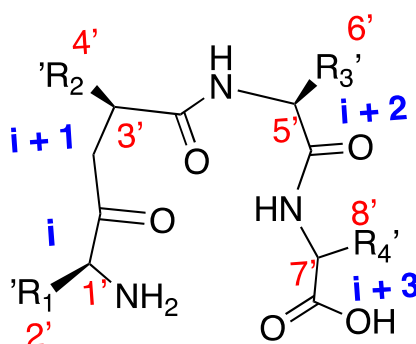
Protein-protein interactions (PPIs) govern many biological processes including proliferation, chemotaxis, endocytosis. They play crucial roles in a range of biological events including gene transcription, cell growth, viral entry into cells and drug resistance.⁷³ Therefore, mis-regulation in PPIs can give rise to a multitude of diseases such as diabetes, HIV and many types of cancers, making PPIs an important target to design novel drugs. However, inhibiting PPIs with small molecules have proven to be rather challenging as protein surfaces are often very large (750 – 4600 Å).⁷⁴ It has been established that many interactions between the larger proteins are facilitated by smaller

protein secondary structural elements. The secondary structural domains can be often recognised by a minimal set of precisely arranged residues that interact on the surface of another protein. Three major secondary structural domains that mediate the PPIs are α -helix, β -turn and β -sheets. There has been substantial effort to design mimetics of these crucial targets.⁷⁵

β -turn motifs are typically composed of four amino acid residues (i , $i+1$, $i+2$, $i+3$ residues). In proteins, β -turns are one of the major secondary structures that reverse the direction of chain propagation and provide a platform for intermolecular interactions with other protein surfaces.⁸³ BZDs were described to be privileged scaffolds due to their ability to mimic β -turns. Figure 1.14 represents structures of a functionalised BZD compound and a β -turn. Through computational modelling it has been shown that the 4 vectors of the BZD derivative 1-2, 3-4, 5-6 and 7-8 (Figure 1.14) correspond to the 4 vectors 1'-2', 3'-4', 5'-6', 7'-8' of a β -turn.⁷⁶ The RMSD (root mean square deviation) values for overlap of the BZD vectors with β -turn vectors were calculated to be less than 1 Å. These findings have later been reconfirmed and extended to suggest that BZD scaffolds are an excellent starting point for designing β -turn mimetics.³⁷



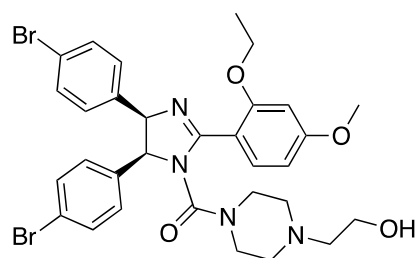
1,4-benzodiazepin-2-one



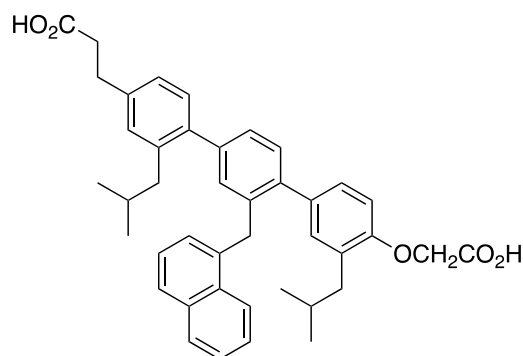
Beta-turn

Figure 1.14: Structures of a BZD and a β -turn

Given the established record of BZD derived β -turn mimetics, chemists looked to expand the range into other protein secondary structural motifs such as the α -helices. Approximately one third to half of all protein secondary structures are comprised of α -helices and thereby frequently found at the interface of PPIs. α -Helix motifs are often composed of 10 residues and 3 turns: i , $i + 3$ or $i + 4$ and $i + 7$ positions. There are *hotspots* in PPIs that span over a small space using a relatively small number of hydrophobic residues, making them attractive druggable targets. Numerous *middle space* (MW = 500 – 1500 Da)⁷⁷ and Lipinski-like (MW < 500 Da) peptidomimetics, mimicking the alpha-helical arrangements which are abundant in such PPI, have been made available, such as terphenyls and nutlins.^{78,79} These molecules typically project the i , $i+3$ or $i+4$ and $i+7$ hydrophobic residues.



Nutlin-2
Leu-Tryp-Phe mimetic
p53-mdm2 target



Hamilton's
Val-Leu-i-Leu mimetic

Figure 1.15: Alpha-helical peptidomimetics

A series of functionalised 1,4-benzodiazepines have also been synthesised as α -helix mimetics. The substituents of functionalised BZDs have proven to be in similar spatial arrangements as the residues on α -helices (i , $i + 3$ or $i + 4$ and $i + 7$) with calculated RMSD value of approximately 1 Å. Tris-substituted 1,4-benzodiazepin-2,5-diones have proven to mimic the side chains of the α -helix motif derived from the tumour suppressor protein p53 and thereby inhibit the PPI between HDM2 and p53. The binding of p53-HDM2 prevents the regular function of p53, therefore, an inhibitor of p53-HDM2 interaction is a potential lead for new cancer therapeutics. Crystallography and NMR studies revealed that optimally functionalised BZD project a similar binding conformation as the α -helix motif of p53.^{75,80,81}

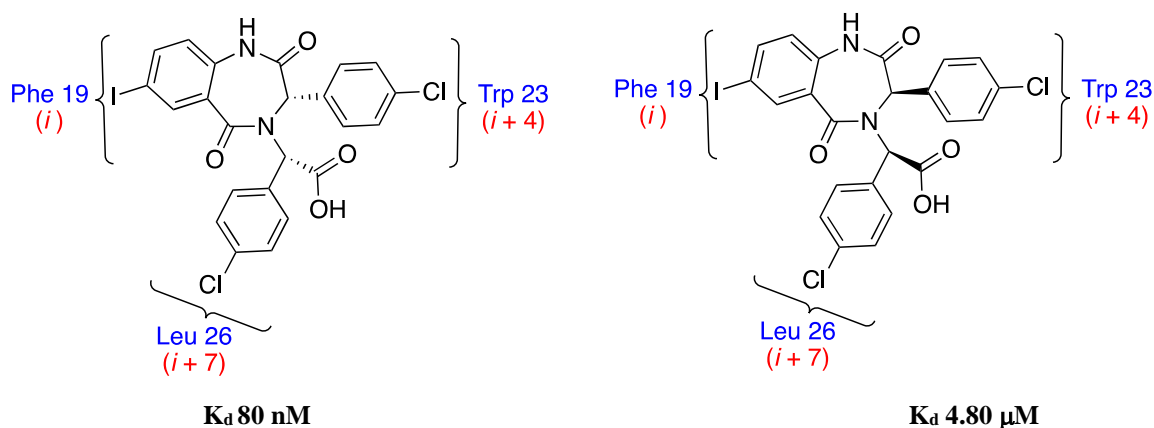


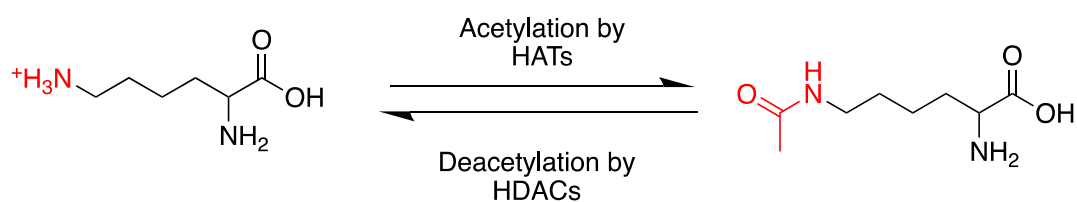
Figure 1.16: Enantiomers of tri-substituted 1,4-benzodiazepin-2,5-diones: P53-HDM2 binding inhibitors

1.4.2 Benzodiazepines in epigenetic targets

Epigenetics with the literal meaning “above genetics”, is the study of heritable changes that occur in post-translational modification (PTM) giving rise to new phenotypes that are not encoded in the DNA sequence.⁸² In other words, epigenetics are heritable changes in the gene expression that do not involve changes in the DNA sequence. Epigenetics play significant roles in the development of diseases and therefore are major targets for developing potential therapeutics.

The basic, positively charged histone proteins pack the negatively charged DNA strands tightly into the nucleus. Approximately 147 base pairs of double-strand DNA are tightly wrapped around a histone octamer to form a nucleosome, the basic unit of chromatin.⁸³ Since 1960, it has been established that histones are modified post-translationally.⁸⁴ PTMs simply refers to modification of proteins that occurs after or during protein biosynthesis. There are a large number of different histone PTMs that perform various crucial roles. These include the regulation of the structure and function of chromatin and recruitment of remodelling enzymes that use the energy from ATP hydrolysis to reposition the nucleosome. Therefore, PTMs not only influence the transcription of DNA, as chromatin is ubiquitous it can also affect many other DNA processes including DNA replication, recombination and repair.⁸⁵

There is a wide range of PTMs such as lysine acetylation, arginine and lysine methylation, proline isomerization and serine/threonine/tyrosine phosphorylation that occur in proteins.⁸⁶ Lysine acetylation is one of the most frequently occurring reversible PTMs in proteins. This process is highly regulated by the opposing effect of two classes of enzymes, histone acetyl transferases (HATs) that generate the acetylation, commonly known as the writing process and histone deacetylases (HDACs) that remove the acetylation, known as the erasing process (Scheme 1.2).⁸⁷ HATs transfer an acetyl group enzymatically from acetyl-coenzyme A (acetyl CoA) to the ϵ -amino group of the lysine side chain on the histone N-terminal tail region.⁸⁸ This process leads to neutralisation of the positively charged histones and thereby weakens interaction between histones and DNA which can cause conformational change and destabilise the nucleosome structure.⁸⁹



Scheme 1. 2: Acetylation and deacetylation process of lysine

1.4.2.1 Bromodomains

Bromodomains (BRDs) are epigenetic reader proteins that recognise the acetyl lysine residues on histones and play a crucial role in the regulation of the transcriptional process.⁸⁸ These proteins were first identified in the 1990s in the *brahma* gene of *Drosophila melanogaster* and are known to be involved with various diseases.⁹⁰ For instance, they are implicated in oncogenic rearrangements that lead to highly oncogenic fusion proteins. Aggressive types of cancer may occur due to the presence of oncogenic fusion proteins. BRDs are also known to be involved in key transcription factors that mediate inflammatory responses. They play vital roles in regulation of the transcription of some viral proteins. Therefore, these proteins are attractive targets for understanding and developing new drugs for diseases such as cancer, inflammation and viral infections.⁸⁸

In the transcriptional process and chromatin reorganisation, BRDs act by translating the chemical modifications executed by HATs and HDACs. Figure 1.17 is the schematic representation of HATs writing the acetylation motif which is read by BRD modules and erased by HDACs.⁹¹

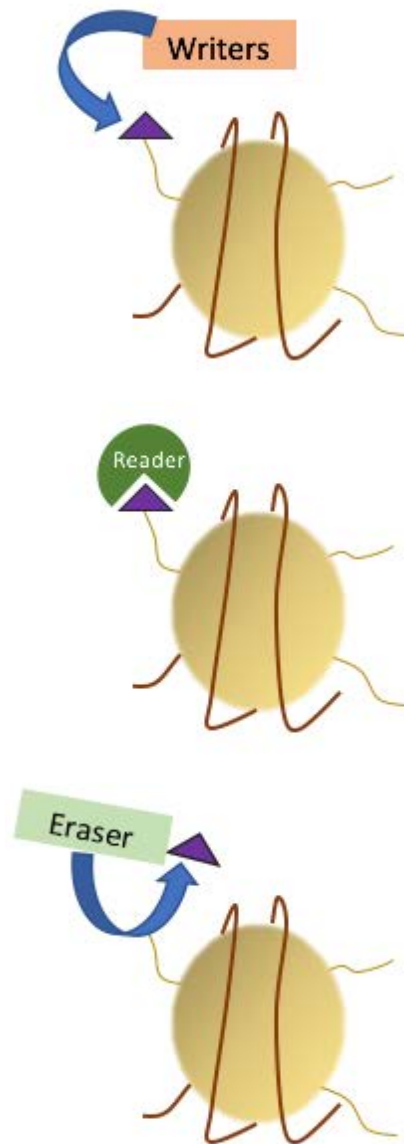


Figure 1.17: HAT (writer) acetylating a lysine side chain on histone, read by a BRD and erased by HDAC

A total of 61 BRDs have been identified in the human proteome that are present in 46 different nuclear and cytoplasmic proteins. The BRDs are classified into 8 subfamilies based on their structural similarities (Figure 1.18). They consist of 110 amino acids that form a highly conserved structure comprised of a left-handed bundle of four α -helices (α Z, α A, α B and α C), linked by flexible loops (ZA and BC loops) that form a hydrophobic pocket with binding sites for acetyl lysine.⁹² Despite the high variations of the loop region, the binding pockets contain highly conserved amino acid residues that

recognise the acetyl lysine motif and form H-bonding in addition to water mediated interactions with the acetyl group. 48 of the 61 BRDs contain an asparagine residue in their bonding pocket that plays a key role in the recognition of acetylated-lysine motif. These are known as typical BRDs. The 13 atypical BRDs contain either a tyrosine, threonine or an aspartic acid in the place of asparagine.^{93,94}

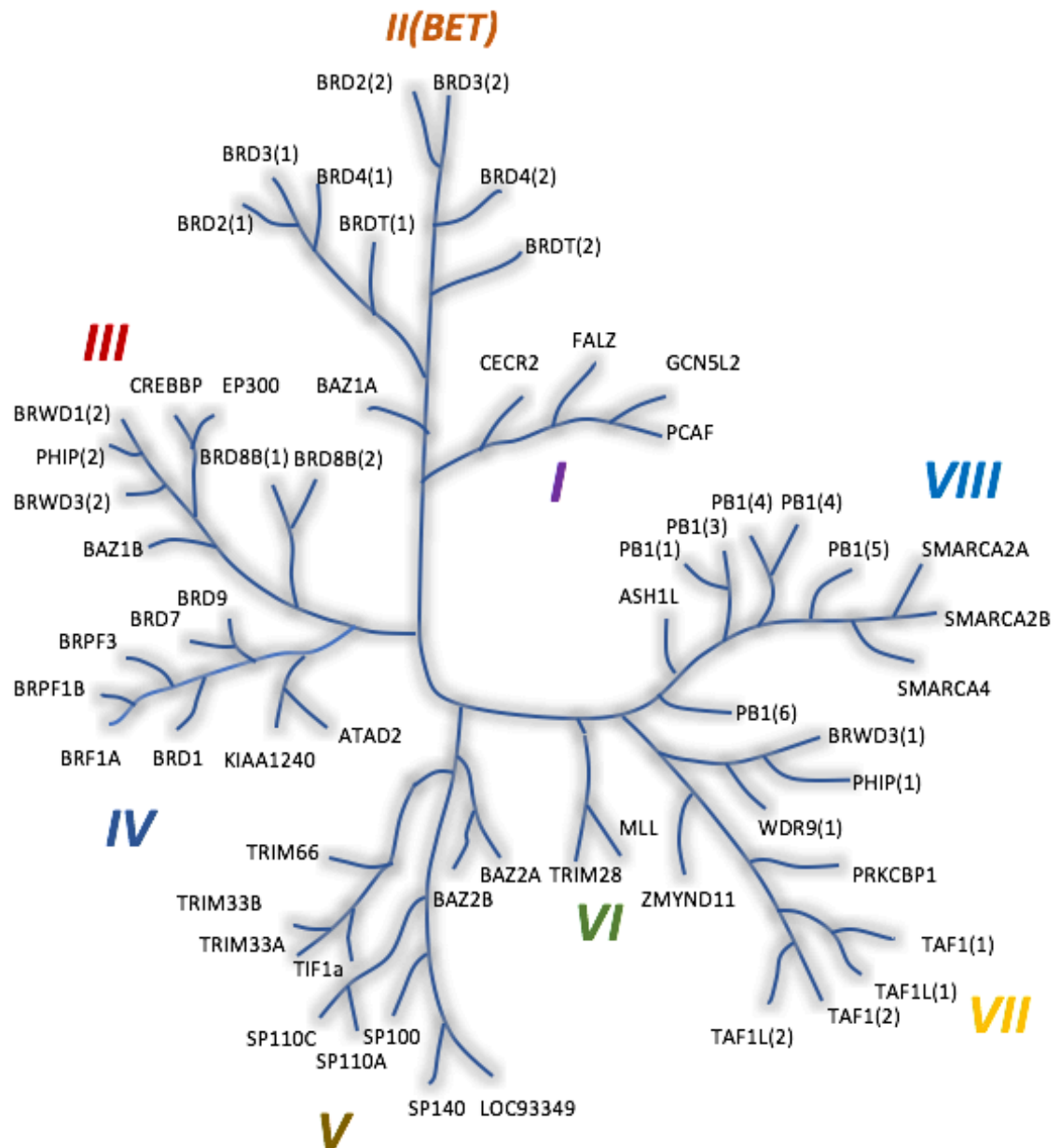


Figure 1.18: Bromodomain family tree with 8 subfamilies (I-VIII)

As mentioned, BRDs are linked with various diseases including many types of cancers.

Both the functions and dysfunctions of BRDs have proved to be involved in the development of diseases. For instance, the human immunodeficiency virus type 1 (HIV-1) *trans*-activator protein Tat, that promotes the viral replication in infected cells, is activated by the binding of human BRD, p300/CBP-associated factor (PCAF) and acetylated lysine residue of Tat.⁹⁵ On the other hand, dysfunctional BRDs have been reported to be involved in diseases, including human squamous carcinoma that is developed due to a fusion protein arising through recurrent chromosomal translocation.⁹⁶

HDAC inhibitors (HDACis) have been targeting many of the mechanisms linked to epigenetic diseases. There are numerous HDAC inhibitors currently used in cancer treatments and some developed for CNS disorders, however, most of these are non-selective.⁹⁷⁻⁹⁹ A better understanding of BRDs in recent years has opened up new opportunities to target these interactions. The interaction between the hydrophobic pocket of the BRDs and the neutral lysine acetyl motif is relatively weak. These interactions can be targeted by small molecules that can interfere with the protein-protein interaction.^{100,101} Combining HDAC inhibitors and BRD inhibitors have proven to be useful strategy in some cases.¹⁰² Numerous BRD inhibitors have been developed in recent years. An overview of the BRD inhibition process is illustrated in Figure 1.19.

The first potent BRD inhibitors were reported by Structural Genomic Consortium (SGC) and the Dana-Faber Cancer Institute,¹⁰³ followed by a second one at the same time from GlaxoSmithKline (GSK).¹⁰⁴ The first potent inhibitors (+)-JQ1, a thieno- 1,4-diazepine and I-BET726, a 1,4-benzodiazepine inhibited BRDs in the bromodomain and extra terminal (BET) family (Figure 1.20).

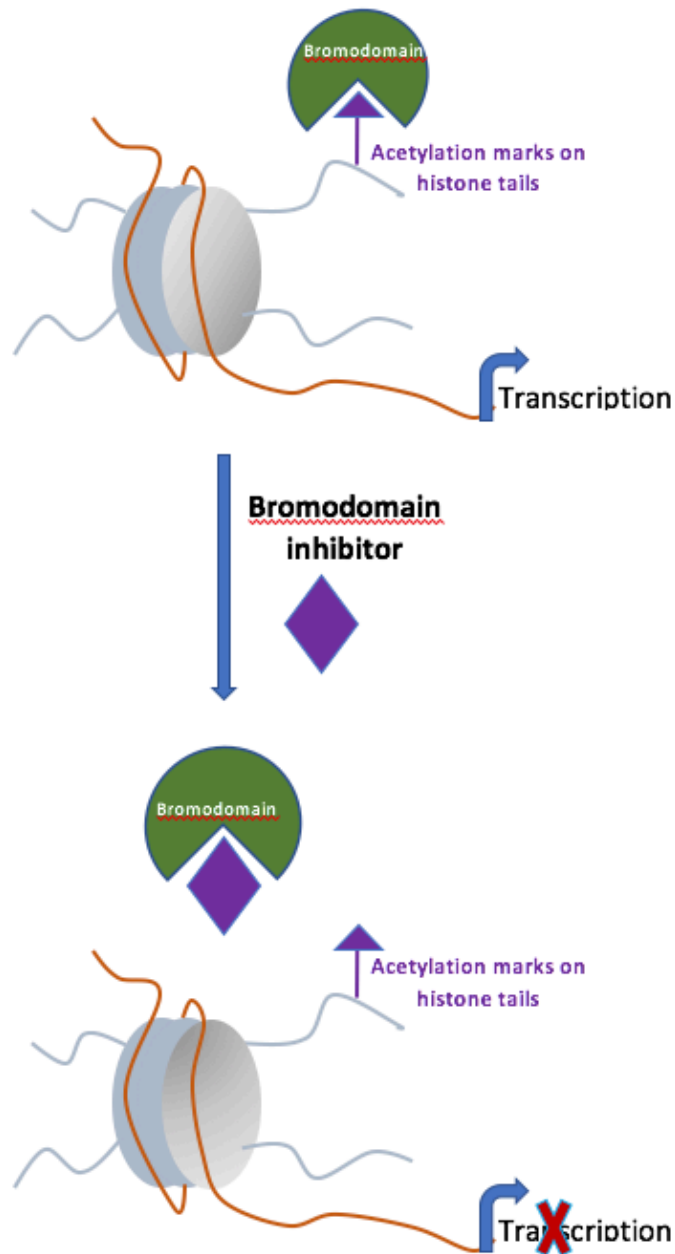


Figure 1.19: Overview of BRD inhibition. Reader proteins BRDs recognise the acetylated lysine motif on histone tails and promote target gene transcription

The BET family consist of BRD2, BRD3, BRD4 and BRDT, which are ubiquitously expressed, except BRDT, which is only expressed in testis. They share common features comprising two amino-terminal BRDs with a binding site for acetylated lysine and a divergent carboxy-terminal recruitment domain.¹⁰⁵ BET BRDs are implicated in several types of cancers, directly involved in the regulation of cancer related genes such as c-

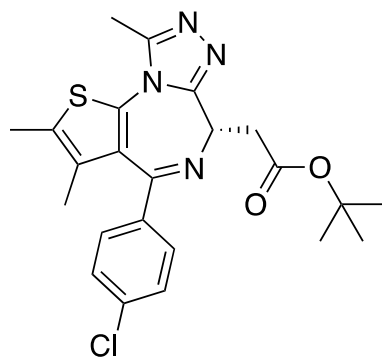
MYC. Inhibiting the binding of BET protein with MYC locus reduces the cell proliferation.^{106,107} The BET family is also involved in cell cycle regulations and BRD4 is known as a global regulator of gene transcription.

High-resolution crystal structures and assay data show that only the (+)-JQ1 enantiomer binds to the acetyl lysine motif. The triazolo-nitrogen of JQ1 forms a hydrogen bond with the asparagine residue, the binding being stabilised by hydrophobic interactions with BET residues. X-ray structures revealed that (+)-JQ1 adopts the conformation that mimics the acetyl-lysine motif and binds to the acetylated lysine binding site occupying the entire binding pocket. (+)-JQ1 was first reported to bind competitively to acetylated lysine binding sites of BRD4 in nuclear protein in testis (NUT) midline carcinoma (NMC). BRD4 forms a fusion oncoprotein with NUT that regulates proliferation and differentiation of aggressive squamous cell carcinoma. (+)-JQ1, the BRD4 inhibitor, produces specific anti-proliferation effect in NMC by displacing the BRD4 oncoprotein.¹⁰³ Subsequently, studies published the efficacy of (+)-JQ1 in various solid tumours such as colon cancer,¹⁰⁸ breast cancer,¹⁰⁹ pancreatic cancer,¹¹⁰ prostate cancer,¹⁰³ lung cancer,¹¹¹ glioblastoma¹¹² and in haematological malignancy.^{113,114}

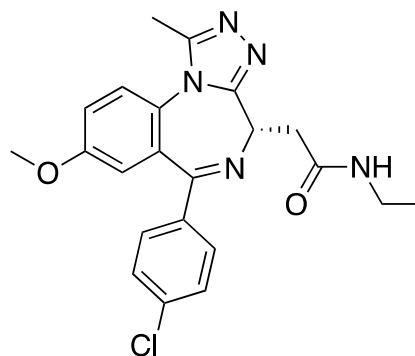
Like JQ1, I-BET726 also binds to the acetyl lysine binding pocket, the important hydrogen bonding interaction of acetyl lysine binding to asparagine residue within the BRD4-bromodomain is mimicked by the triazole ring of I-BET726.¹⁰⁴ This BZD based structure also reduces the growth of NMC-malignant cells. GSK started clinical trials of I-BET726 for the treatment of NMC malignancy and subsequently extended this to other types of cancer such as colorectal cancer, lung cancer, breast cancer and MYCN driven solid tumour subjects.

Other BZD based BET bromodomain inhibitors include OTX015 and CPI203. OTX015 is a BRD2, 3 and 4 inhibitor with stronger anti-proliferation effects than (+)-JQ1 and a substantial anti-tumour effect in glioblastoma mouse models.¹¹⁵ It also shows similar effects as (+)-JQ1 in leukemic cell lines where it inhibits the cell growth and leads to apoptosis. OTX015 is undergoing six clinical trials currently for several types of cancer such as NMC, glioblastoma and pancreatic ductal carcinoma.¹⁰⁵ CPI203 is still at the preclinical stage but shows similar activities with some clinically approved drugs for

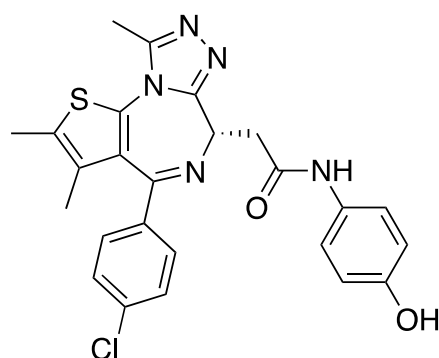
cancer treatment. For instance, it downregulates MYC expression and inhibits cell proliferation in pancreatic neuroendocrine tumours (PanNET).¹¹⁶



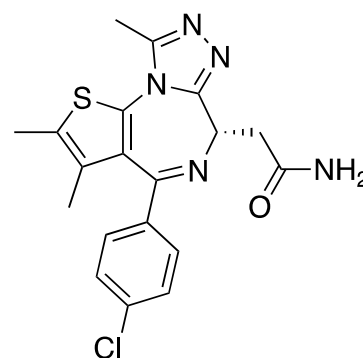
(+)-JQ1



I-BET726



OTX-015



CPI-203

Figure 1.20: Structures of selective BZD based BET-bromodomain inhibitors

As stated, HDAC inhibition is another attractive strategy to target epigenetic associated diseases such as cancer, inflammation and CNS disorders. So far, 18 different human HDACs have been identified, 11 of which are Zn^{2+} dependent and known as the classical HDACs. The rest structurally distinct, silent information regulator related proteins (sirtuins) are NAD^+ dependent. The classical HDACs are further divided into three classes: class I, consisting of HDACs 1, 2, 3 and 8, class IIa comprises HDACs 4, 5, 7, 9, class IIb HDACs 6, 10 and class IV HDAC 11. Class III belongs to the sirtuins comprising

sirt1 to sirt7.¹¹⁷ A significant effort in the past decade has resulted in a number of clinically approved HDACis in the market. These include the hydroxamic acid, vorinostat (SAHA),^{118–121} the cyclic peptide, romidepsine,^{122–125} the hydroxamate, Belinostat^{126–128} and the most recently approved in 2015, Panobinostat (LBH589 or Farydak®) for the treatment of multiple myeloma (Figure 1.21).^{129,130}

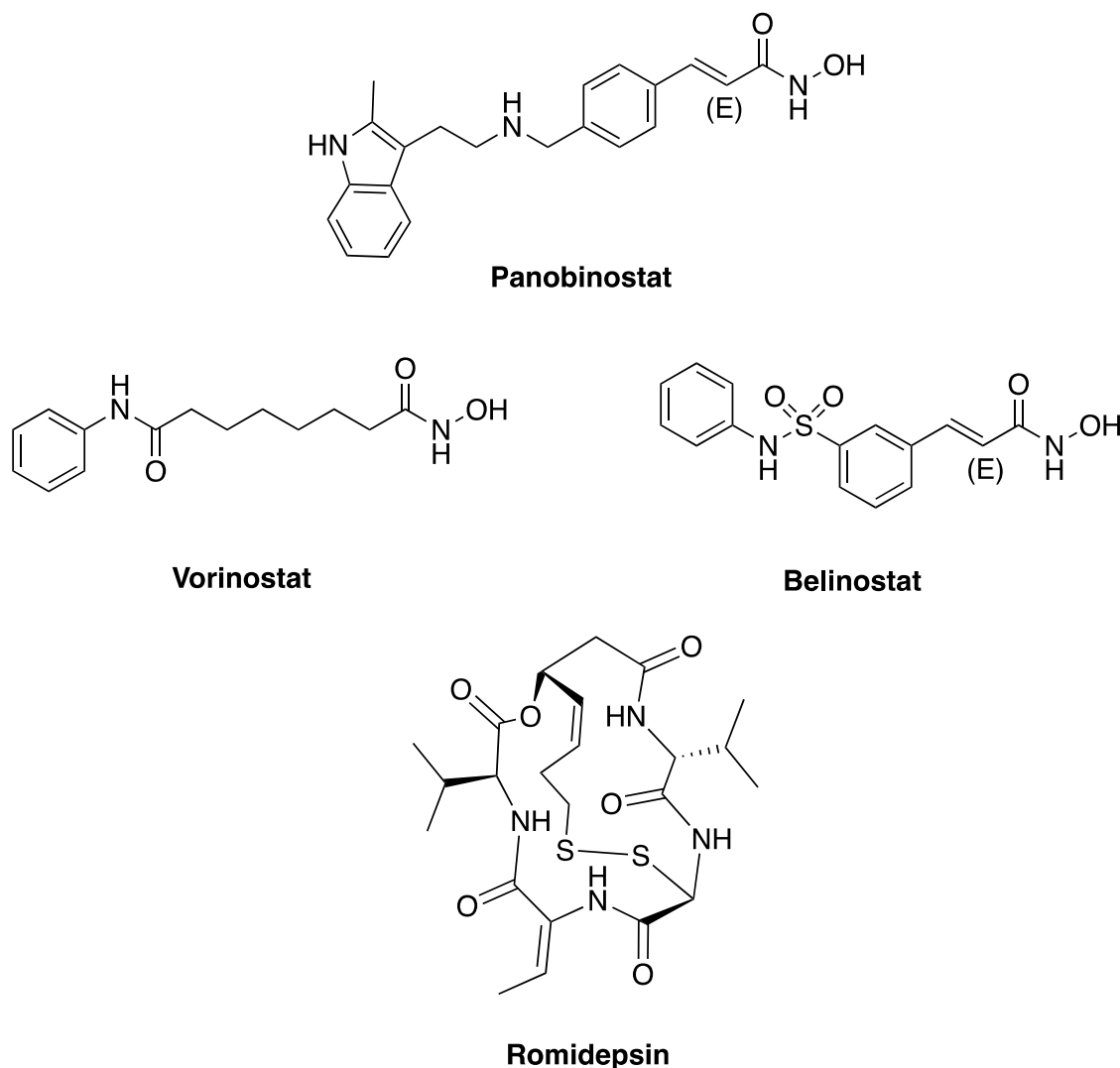


Figure 1.21: Structures of selected clinically approved HDACis

However, there is still a genuine need for improved HDACis as most of the known ones lack selectivity and specificity, and this leads to various undesired side effects.¹¹⁷ In recent years, a number of BZD-based HDAC inhibitors have been reported. Classical HDACis typically comprise of a chelating moiety (often a hydroxamate group) that is able to chelate the Zn^{2+} located below the active site, connected through a suitable chain-linker

to a hydrophobic recognition motif (cap) that can bind at the enzyme surface. BZD-based HDACis have been reported where the BZD ring acts as the cap. Although BZD-based HDACis are still at the developmental stage, studies are showing promising aspects for generating highly potent and selective BZD derivatives as selective HDACis. There have been substantial efforts to design potent HDACis based on a hybridization between clinically approved structures such as SAHA and the 5-phenyl-1,4-benzodiazepine moiety, with the BZD acting as an aryl cap (the NHOH is deprotonated to NHO^- , which binds to Zn^{2+}). For instance, **1.3** shows similar inhibitory activities to SAHA against HDAC 1 and HDAC 6 (Figure 1.22).^{131,132}

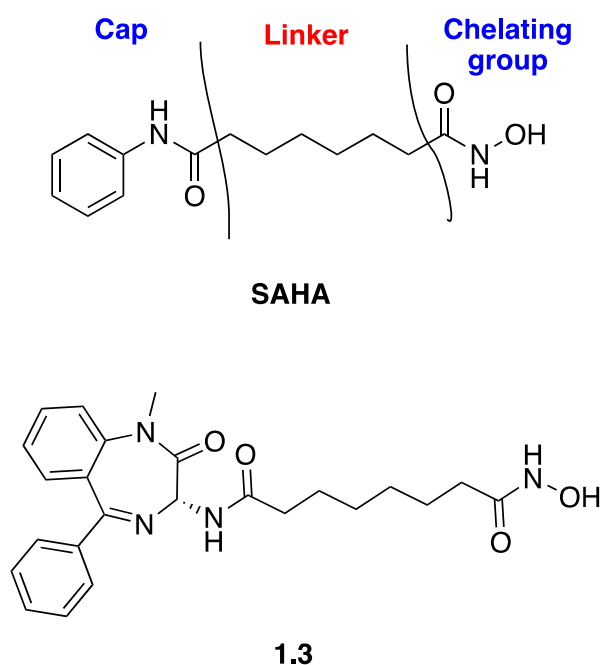


Figure 1.22: HDACi **1.3** - hybrid between SAHA and a 5-phenyl-1,4-benzodiazepine-2-one

Compound **1.4** in Figure 1.23 was reported to show HDAC inhibitory activity and antiproliferative against non-small lung cancer cell line H661. A number of similar BZD analogues were prepared which showed low micro molar activity in H661 cells.¹³³

Figure 1.23: 1,4-benzodiazepine-2,5-dione-based HDAC inhibitor (IC_{50} 6 μ M) with antiproliferative activities in H661 cells.

O=C(O)NCCCCN1C(=O)C(S)N=C2C1c1ccccc1C2c3ccccc3NC(=O)CCCCN1C(=O)N(C2=CC=CC=C2C3=CC=CC=C3C1=N2)CCNC(=N)N

1.6

Table 1.1: HDAC IC₅₀ (μM) values of BZD analogues

	HDAC IC ₅₀ (μM)			
	1	3	6	8
1.5	0.46	0.18	0.58	8.11
1.6	1.44	0.22	2.63	>30

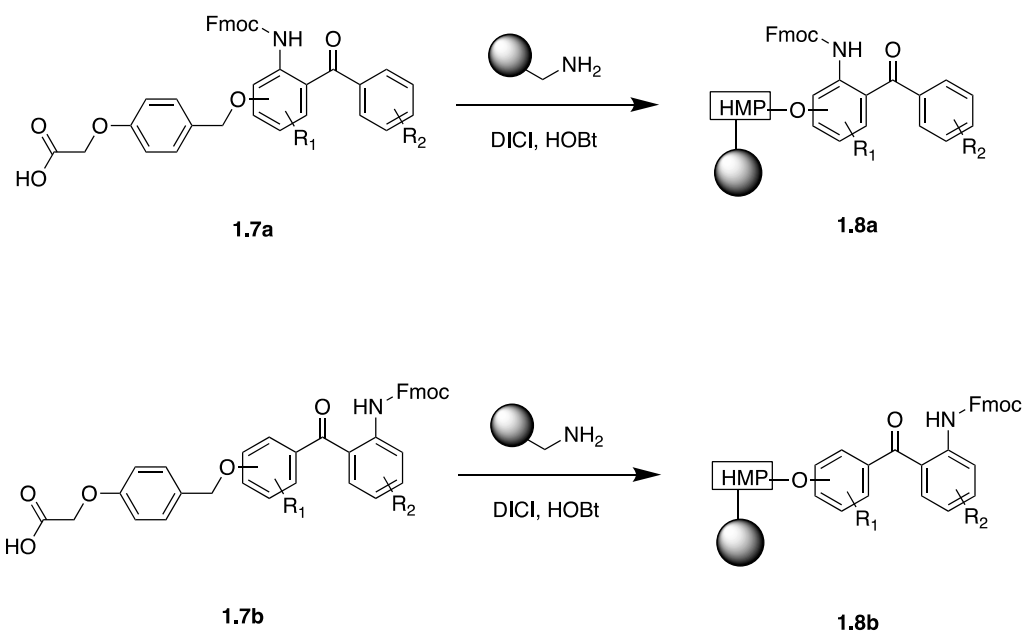
The above discussion demonstrates BZDs' potency in a diverse array of proteins. Due to their usefulness in treating various diseases, this project took the notion that BZDs can be an effective starting point to develop new therapeutics including addressing currently undruggable protein targets. Therefore, a major part of the project focuses on developing effective, step and atom-economic protocols to synthesise libraries of BZD analogues.

1.5 Synthesis routes, limitations & the project aims

Over the last four decades, major efforts have been focused on developing various routes to synthesise 1,4-benzodiazepin-2-one analogues. The following paragraphs highlight some of the selected synthetic routes in this area and look into the limitations of current approaches for the rapid synthesis of BZD-based libraries. Subsequently, drawing from these limitations and taking consideration the potency of BZDs, this introductory Chapter concludes with a brief discussion on the aims of this body of work.

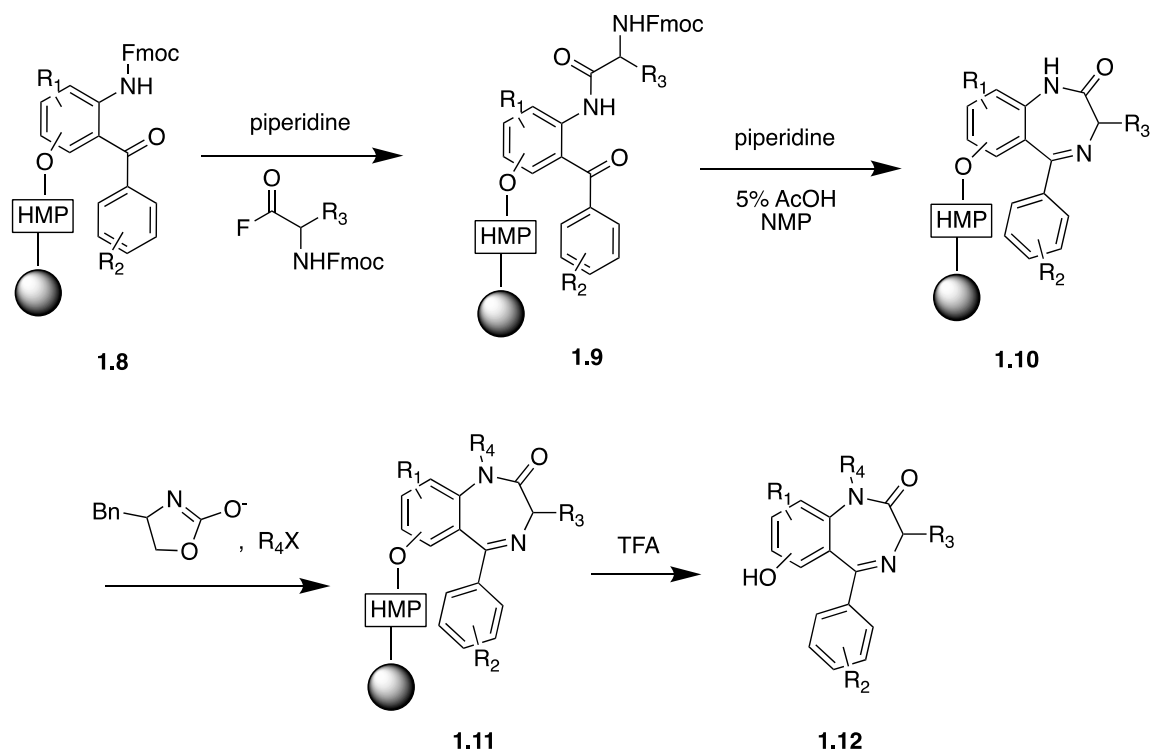
1.5.1 Solid-phase synthesis

The solid-phase synthesis approach was originally developed by Robert Bruce Merrifield to synthesise peptide molecules. In this process, the reactant is bound to an insoluble material and synthesised step-by-step in reactant solution. Excess reagents and by-products can be easily removed and purified by washing. Ellman *et al.* reported the solid-phase synthesis of 1,4-benzodiazepin-2-ones where they synthesised the derivatives from three different components: amino acids, 2-aminobenzophenones and alkylating agents. Functionalised *N*-Fmoc aminoenzophenones are coupled with 4-hydroxymethylphenoxyacetic acid (HMP) cleavable linker.^{134,135} As shown in Scheme 1.2, the HMP linker may be coupled through a carboxyl or hydroxyl group on either phenyl ring of the 2-aminobenzophenone. Support-bound starting material **1.8a** and **1.8b** are then synthesised by coupling the linker-substituted 2-aminobenzophenones **1.7a** and **1.7b** to the solid support using standard amide-bond coupling methods.



Scheme 1.3: The amide coupling of linker-substituted aminobenzophenones **1.7a**, **1.7b** to the solid support.

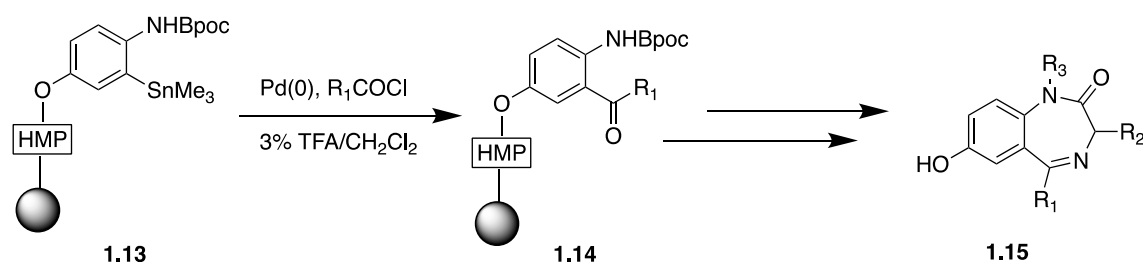
The Fmoc protecting group is removed from **1.8** by treating with piperidine in DMF to initiate the synthesis of BZD derivatives. The resulting unprotected aminobenzophenone is coupled to an α -N-Fmoc amino acid fluoride as presented in Scheme 1.4. Due to the poor nucleophilicity of 2-aminobenzophenones, regular activation methods for solid-phase peptide synthesis are not successful in this coupling step. However, the activated R- α -N-Fmoc amino acid fluorides developed by Carpino *et al.* proved to be effective, even for electron-deficient 2-aminobenzophenones, in this coupling step to yield the amide product **1.9** (Scheme 1.4).^{136,137} The amine is deprotected by removing the Fmoc group by treatment with piperidine. The resulting free amine is further treated with 5% acetic acid in *N*-methylpyrrolidinone (NMP) at 60 °C to afford **1.10**, which can subsequently be alkylated using an excess of a base that is basic enough to fully deprotonate the anilide. Lithiated acetanilide or lithiated 5-(phenylmethyl)-2-oxazolidinone are generally employed in this step to provide the fully functionalised 1,4-benzodiazepines **1.11**. The final benzodiazepine products **1.12** is afforded in high yield by treatment with acid cleavage cocktail trifluoroacetic acid (TFA)/dimethyl sulphide/H₂O (95:5:5).^{138–140}



Scheme 1.4: Solid-phase synthesis of 1,4-benzodiazepin-2-one derivatives

Additionally, Ellman *et al.* employed a Stille coupling reaction to synthesise a variety of aminoaryl ketones on solid support, in order to increase the diversity of 1,4-benzodiazepines prepared *via* solid-phase synthesis. The Stille coupling is particularly advantageous as it requires mild conditions, tolerates a diverse functionality and a wide range of commercially available acid chlorides, which are compatible with the BZD synthesis protocol, although tin reagents are rather toxic.^{141,142}

There are five steps involved in preparing 2-(4-biphenyl)isopropoxyloxycarbonyl (Bpoc) protected (aminoaryl) stannane **1.13** from commercially available substances. HMP linker is generally employed for solid support and the reaction is carried out using a diverse range of acid chlorides in the presence of the catalyst $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$. The Bpoc group is removed from **1.14** by quick treatment with 3% TFA in dichloromethane (DCM). The 1,4-benzodiazepine analogues **1.15** are then synthesised from the deprotected support-bound aminoaryl ketone according to previously described synthesis route.



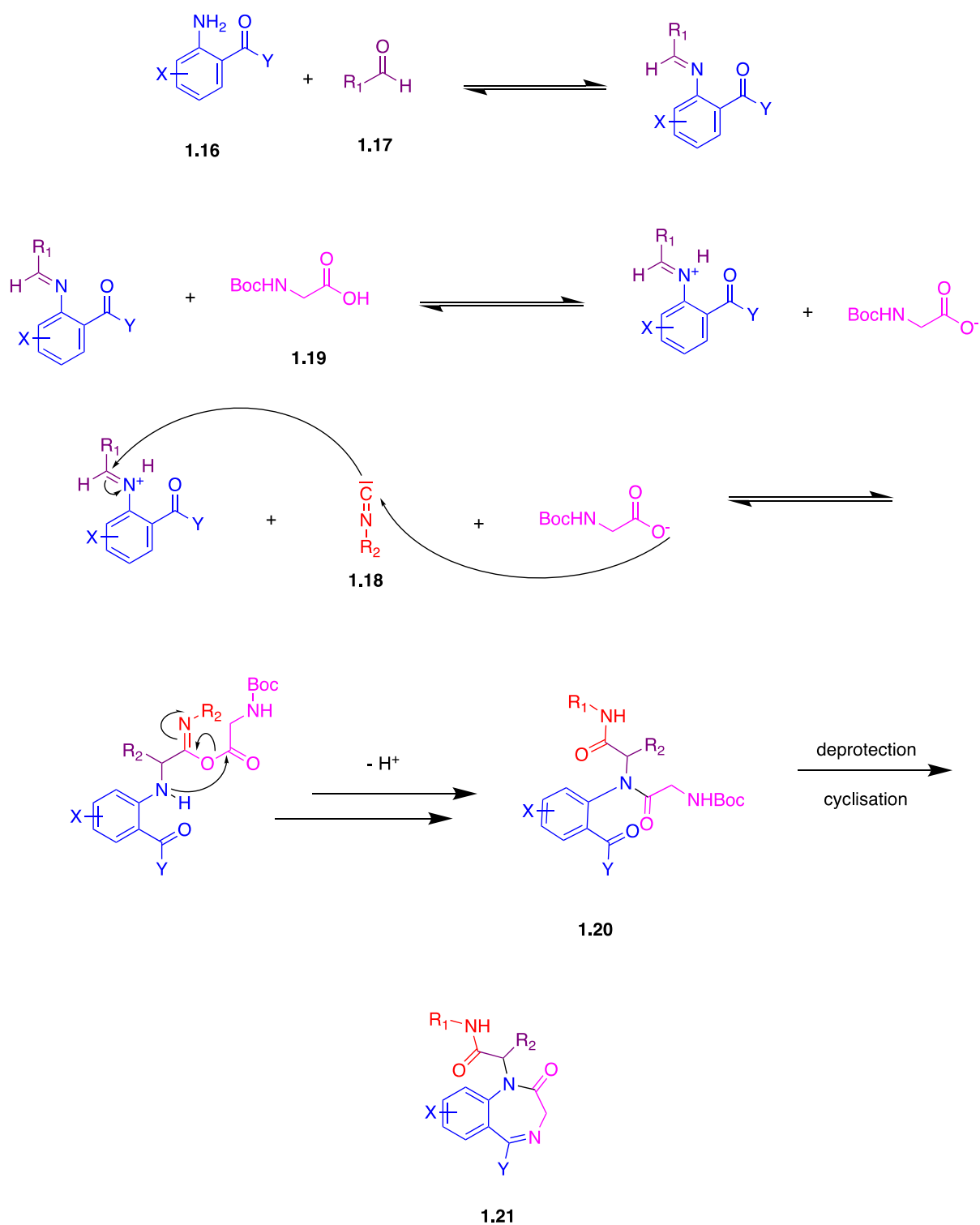
Scheme 1.5: Stille coupling reaction employed for synthesis of aminoaryl ketones **1.14**

Although this synthetic route is more versatile with respectable yields ranging from 52% to 82%, it is a lengthy process requiring over 10 steps.^{143,144}

1.5.2 Multicomponent synthesis

A multicomponent reaction (MCR) is a versatile synthetic way to develop a diverse range of substituted heterocyclic molecules. Among the various routes employed in synthesising libraries of substituted 1,4-benzodiazepin-2-ones the isocyanide-based MCRs are certainly noteworthy. The Ugi four-component reaction (Ugi-4CR) is the key step of such MCRs. The reactions are performed with anthranilic or *N*-Boc protected anthranilic acids, aldehydes and convertible isocyanides. Bifunctional reagents such as ethyl glyoxylate, *N*-Boc- α -aminoaldehydes, α -amino acid esters, and *N*-Boc-1,2-diaminoethanes have been used in alternative Ugi-4CR syntheses of BZDs.^{145–147}

Scheme 1.6 shows that a 1,4-benzodiazepin-2-one derivative **1.21** synthesised by a Ugi-4CR, followed by deprotection and cyclisation steps. The substituted aminophenyl ketone **1.16** performs as an amine component in the Ugi-4CR. The mechanism is proposed to involve the formation of an imine with by condensation of the amine with the aldehyde **1.17**. This is followed by the addition of the carboxylic acid and imino carbon across the isocyanide carbon. The resulting acylated isoamide undergoes further rearrangement to afford the Ugi product **1.20**. The next step involves removing the Boc-group from the Ugi product **1.20**, which then undergoes condensation with the orthogonal ketone group to afford the 1,4-benzodiazepine derivatives **1.21** in the cyclization step.

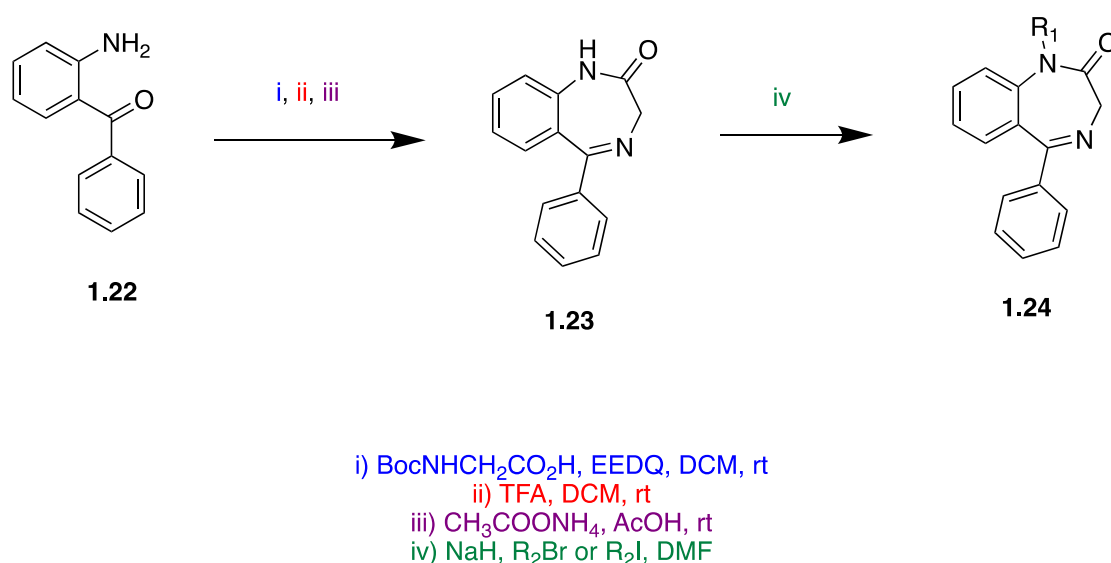


Scheme 1.6: Multicomponent synthesis of BZDs

It is noteworthy that the reaction occurs in one-pot, i.e., the crude Ugi product **1.20** is not isolated, rather treated with TFA in 1,2-dichloroethane (DCE) *in situ* to give the final product.¹⁴⁵

1.5.3 Multi-step synthesis method

Spencer *et al.* reported a three-step synthesis of substituted BZD derivative **1.23** by modifying previous protocols using the coupling reagent 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ).^{138,149} The readily available 2-aminobenzophenone is coupled with Boc-NHCH(R₂)CO₂H at room temperature.



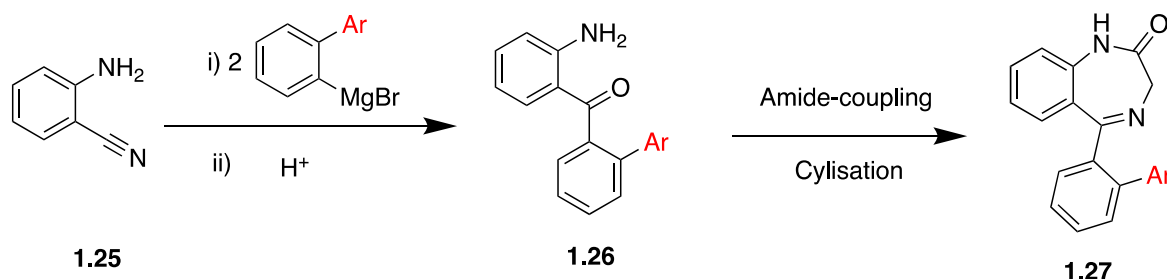
Scheme 1.7: A multi-step synthesis method for 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

The carbonyl group in the BocNHCH(R₂)CO₂H undergoes an amide coupling with the amino group in the ortho- keto aniline **1.22** and undergoes further cyclisation to form a seven-membered ring, with the aid of EEDQ coupling agent resulting in the BZD analogues **1.23**. **1.23** can be further functionalised by alkylating at the N-1 position. **1.24** is achieved by treating **1.23** with sodium hydride and then alkylating with appropriate alkyl or benzyl halide.^{73,150}

1.6 Limitations for efficient library synthesis of BZD analogues

The efficiency in rapid library synthesis of privileged scaffolds such as BZDs is still extremely desirable in medicinal chemistry as many of the BZD synthesis routes require several steps making it inefficient for library generation. For instance, a typical route for

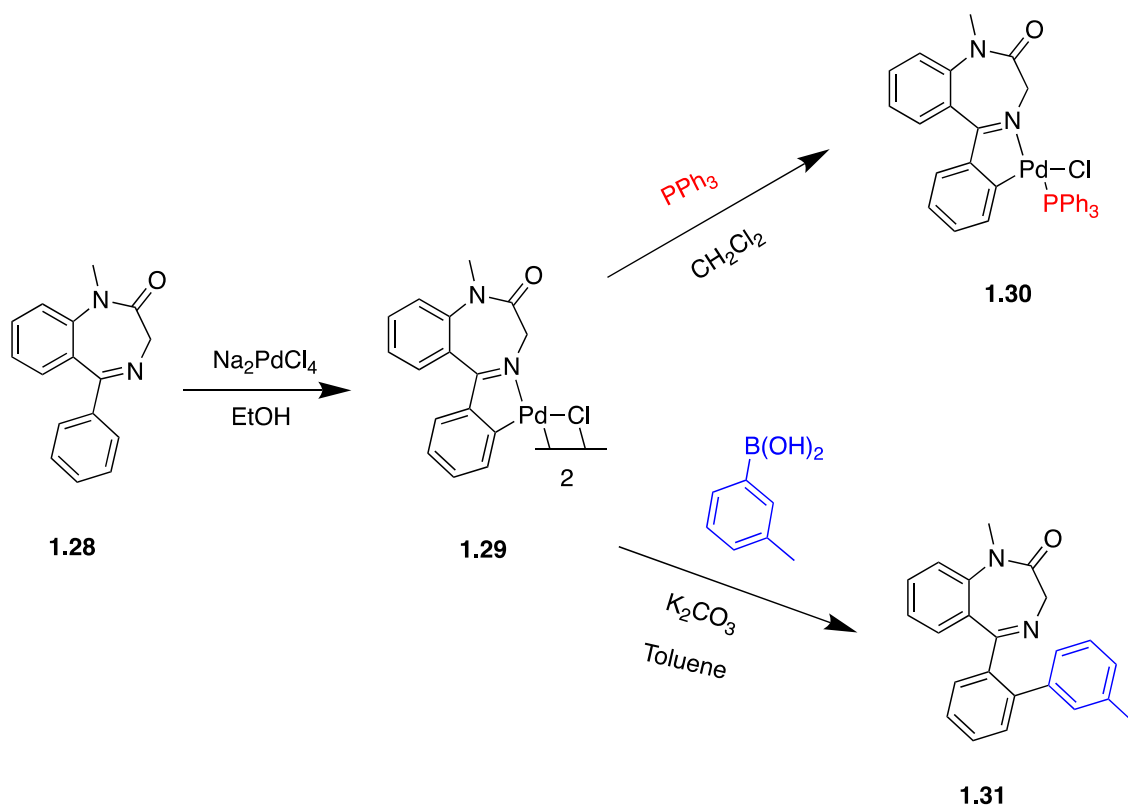
functionalising at the C-5 position requires several repetitive steps as shown in Scheme 1.8.



Scheme 1.8: A typical synthetic route to 5-(2-arylohenyl)-1,3-hydro-2H-1,4-benzodiazepin-2-one

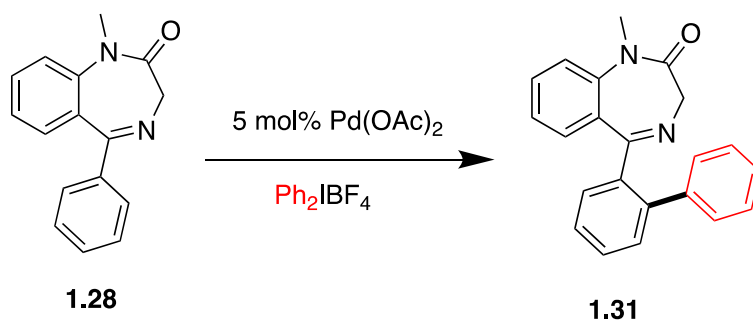
The reaction starts with the aniline **1.25** and two equivalents of appropriate Grignard reagent. It requires cold temperature, dry conditions and an acidic workup to yield the ortho-keto aniline **1.23**, which further undergoes coupling and cyclisation steps as described in Scheme 1.7 and 1.8. Therefore, library generation of varying ortho-substituted BZDs becomes inefficient since such groups need to be introduced early in the synthetic sequence followed by repetitive coupling and cyclisation steps every time.

In an attempt to address this issue, Spencer *et al.*, have previously reported a synthetic route for ortho-substituted BZDs (Scheme 1.9). Firstly, BZD-based palladacycles were synthesised by C-H activation and treating **1.28** with Na_2PdCl_4 in ethanol resulting in the palladacycle **1.29**. The insoluble palladacycle affords the soluble product **1.30** by treatment with triphenylphosphine in DCM, which could be fully characterised by e.g. ^1H NMR and X-ray crystallography. **1.28** underwent stoichiometric reaction with arylboronic acid (Scheme 1.9) to afford the ortho-arylated BZD analogue **1.31**.¹⁵²



Scheme 1.9: Ortho-arylated BZD analogue from BZD-based palladacycles

Subsequently, the group was able to undertake preliminary steps towards the synthesis of ortho-arylated BZDs using a palladacycle in a catalytic C-H activation. The catalytic reaction employed 1.5 equivalent of diaryliodonium tetrafluoroborate, 5 mol% palladium (II) acetate in acetic acid at 100 °C for 12 hours with the highest conversion rate of 61%. However, the product proved to be inseparable from starting material and potential side products (Scheme 1.10) using standard column chromatography.¹⁵¹



Scheme 1.10: Attempted ortho-arylation of BZD by catalytic C-H activation

1.7 Thesis aims

Following from the above discussion, it can be argued that despite the commercial availability and the traditional synthetic routes for 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one skeletons, one-step synthetic routes for BZD-based library generation are yet to be successfully developed. Therefore, this project seeks to explore the possibility and scope for efficient and atom economical BZD-based library generation routes avoiding any repetitive steps. In doing so, the project initially focused on the ortho-arylation (introduction of **R₁**) following on from our previous work.¹⁵¹ Subsequently, it explores the scopes for one-step *N*-arylations as shown in Figure 1.25 (**R₁**, **R₂**).

N-alkylation/arylation

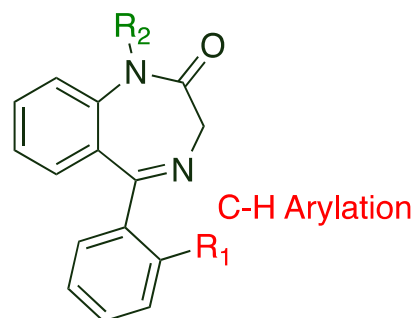


Figure 1. 25: Functionalisation scopes of BZD skeleton for library generation

In Chapter 2, microwave irradiation is employed rather than thermal heating. Although microwave chemistry involves a high equipment cost, the benefits of controlled microwave heating are manifold:^{152–157}

- It significantly reduces the reaction times, often with higher yields and fewer side reactions.
- The reaction can be heated at higher temperatures and the choice of solvent is not dependent on its boiling point but rather on the dielectric properties of the reaction medium. This can be easily adjusted by addition of ionic liquids.
- The overall process is more energy efficient than thermal heating, since the whole reaction medium is heated simultaneously as opposed to thermal heating where, reaction mixture in contact with the vessel is heated first (Figure 1.26).

- Microwave irradiation is amenable to parallel and automatic sequential processing format.

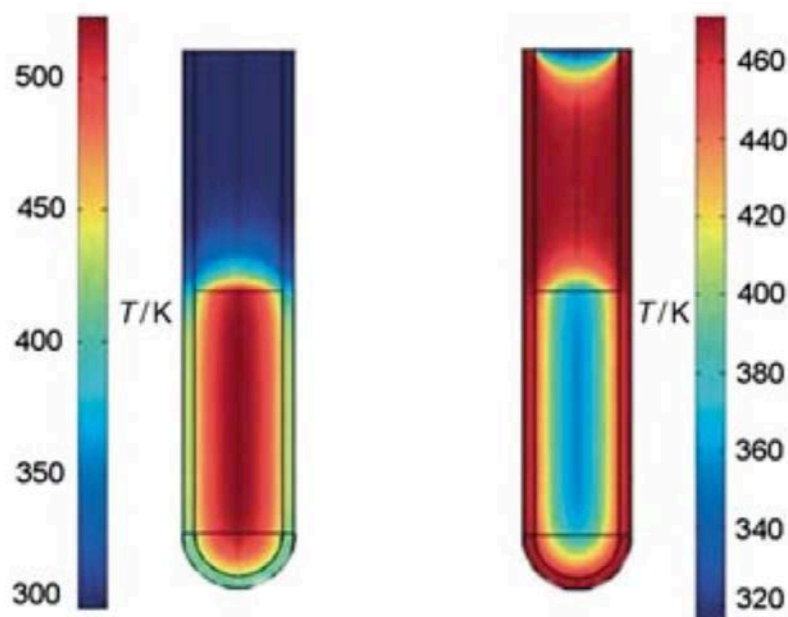
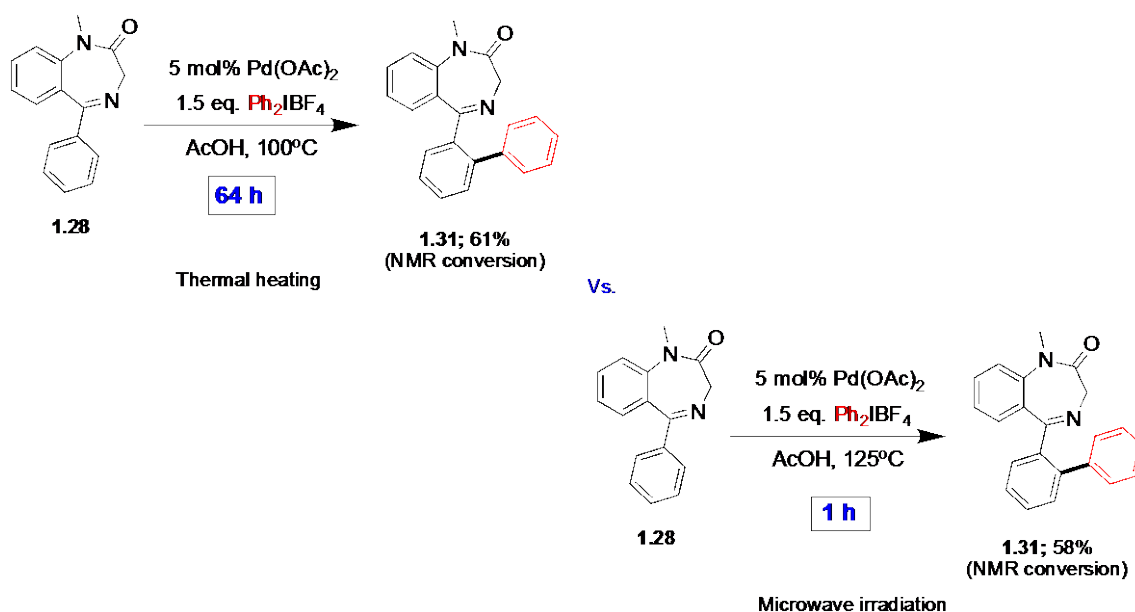


Figure 1. 26: Microwave heating (left) vs Thermal heating (right) after 60 seconds¹⁵³

Therefore, higher efficiency in library generation of ortho-arylated BZDs is anticipated to be achieved by microwave heating. The comparison of thermal heating vs microwave is shown in Scheme 1.11.



Scheme 1.11: Reaction time in conventional heating vs. microwave heating for synthesis of C-H arylated BZDs

1.8 References

- 1 L. Brunton, B. Chabner and B. Knollman, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, The McGraw-Hill, New York, 12th edn., 2013, vol. 53.
- 2 R. I. Shader, D. J. Greenblatt and M. B. Balter, *J. Clin. Pharmacol.*, 1991, **31**, 781–784.
- 3 M. Lader, *Neuroscience*, 1978, **3**, 159–165.
- 4 M. Lader and H. Petursson, *Neuropharmacology*, 1983, **22**, 527–533.
- 5 W. H. Trethowan, *Br. Med. J.*, 1975, **3**, 749–751.
- 6 K. W. Chen, C. C. Berger, D. P. Forde, C. D'Adamo, E. Weintraub and D. Gandhi, *BMC Psychiatry*, 2011, **11**, 111–118.
- 7 Stefan Braese, *Privileged Scaffolds in Medicinal Chemistry*, Royal Society of Chemistry, Cambridge, 2016, 15–35.
- 8 G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 1968, **68**, 747–784.
- 9 E. Reeder and L. H. Sternbach, *J. Org. Chem.*, 1961, **26**, 4936–4941.
- 10 L. H. Sternbach, S. Kaiser and E. Reeder, *J. Am. Chem. Soc.*, 1960, **82**, 475–480.

- 11 E. Berényi and G. Blaskó, *Acta Pharm. Hung.*, 1993, **63**, 45–51.
- 12 L. H. Sternbach, *Agents Actions*, 1994, **43**, 82–85.
- 13 L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *J. Org. Chem.*, 1962, **27**, 3788–3796.
- 14 L. Sternbach, *Angew. Chemie Int. Ed. English*, 1971, **10**, 34–43.
- 15 M. Lader, *Aust. Nz. J. Psychiat.*, 1981, **15**, 1-9.
- 16 S. V. Argyropoulos and D. J. Nutt, *Eur. Neuropsychopharmacol.*, 1999, **9**, 407–412.
- 17 De Taylor, *The Benzodiazepines in current clinical practice*, Royal Society of Medicine, London, 1987.
- 18 J. F. Rosenbaum, *J. Clin. Psychiatry*, 2005, **66**, 4–8.
- 19 M. B. King, *Br. J. Gen. Pract.*, 1992, **42**, 202–205.
- 20 K. A. Jones, S. Nielsen, R. Bruno, M. Frei and D. I. Lubman, *Aust. Fam. Physician*, 2011, **40**, 862–865.
- 21 D. S. Baldwin, K. Aitchison, A. Bateson, H. V. Curran, S. Davies, B. Leonard, D. J. Nutt, D. N. Stephens and S. Wilson, *J. Psychopharmacol.*, 2013, **27**, 967–971.
- 22 C. H. Ashton and C. H. A. Dm, in *Benzodiazepines: how they work and how to withdraw*, Newcastle University, Newcastle, 2011, pp. 5–6.
- 23 W. Schallek, W. D. Horst and W. Schlosser, *Advances in Pharmacology and Chemotherapy*, Academic Press, New Jersey, 1979.
- 24 P. S. Miller and A. R. Aricescu, *Nature*, 2014, **512**, 270–275.
- 25 S. G. Brickley and I. Mody, *Neuron*, 2012, **73**, 23–34.
- 26 W. M. Connelly, A. C. Errington, G. Di Giovanni and V. Crunelli, *Front. Neural Circuits*, 2013, **7**, 1-8.
- 27 T. Z. Deeb, J. Maguire and S. J. Moss, *Epilepsia*, 2012, **53**, 79–88.
- 28 W. Hevers and H. Lüddens, *Mol. Neurobiol.*, 1998, **18**, 35–86.
- 29 H. Stefanits, I. Milenkovic, N. Mahr, E. Patariaia, J. A. Hainfellner, G. G. Kovacs, W. Sieghart, D. Yilmazer-Hanke and T. Czech, *J. Comp. Neurol.*, 2018, **526**, 324–348.
- 30 W. T. Ralvenius, D. Benke, M. A. Acuña, U. Rudolph and H. U. Zeilhofer, *Nat. Commun.*, 2015, **6**, 1-12.
- 31 H. Möhler, J. M. Fritschy and U. Rudolph, *J. Pharmacol. Exp. Ther.*, 2002, **300**, 2–8.
- 32 D. J. Greenblatt, R. I. Shader, M. Divoll and J. S. Harmatz, *Br. J. clin. Pharmac.*,

- 1981, **11**, 11–16.
- 33 W. A. Ray, M. R. Griffin and W. Downey, *JAMA J. Am. Med. Assoc.*, 1989, **262**, 3303–3307.
 - 34 C. E. Griffin, A. M. Kaye, F. R. Bueno and A. D. Kaye, *Ochsner J.*, 2013, **13**, 214–223.
 - 35 W. Lorman, *J. Addict. Nurs.*, 2017, **28**, 96–97.
 - 36 H. Valerie Curran, *Psychopharmacology (Berl.)*, 1991, **105**, 1–8.
 - 37 W. C. Ripka, G. V. De Lucca, A. C. Bach, R. S. Pottorf and J. M. Blaney, *Tetrahedron*, 1993, **49**, 3609–3628.
 - 38 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235–2246.
 - 39 B. E. Evans, M. G. Bock, K. E. Rittle, R. M. DiPardo, W. L. Whitter, D. F. Veber, P. S. Anderson and R. M. Freidinger, *Proc. Natl. Acad. Sci. U. S. A.*, 1986, **83**, 4918–4922.
 - 40 R. Chandra and R. A. Liddle, 2007, **14**, 63–67.
 - 41 R. A. Liddle, *Annu. Rev. Physiol.*, 1997, **59**, 221–242.
 - 42 X. Dong, C. Wang, J. Zhang, S. Wang, H. Li, Y. Kang, S. Tian and L. Fu, *Cell. Physiol. Biochem.*, 2017, **43**, 2479–2488.
 - 43 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235–2246.
 - 44 M. G. Bock, R. M. DiPardo, B. E. Evans, K. E. Rittle, W. L. Whitter, D. F. Veber, R. M. Freidinger, R. S. Chang, T. B. Chen and V. J. Lotti, *J. Med. Chem.*, 1990, **33**, 450–455.
 - 45 M. G. Bock, R. M. DiPardo, B. E. Evans, K. E. Rittle, W. L. Whitter, V. M. Garsky, K. F. Gilbert, J. L. Leighton, K. L. Carson, E. C. Mellin, D. F. Veber, R. S. L. Chang, V. J. Lotti, S. B. Freedman, A. J. Smith, S. Patel, P. S. Anderson and R. M. Freidinger, *J. Med. Chem.*, 1993, **36**, 4276–4292.
 - 46 G. A. Showell, S. Bourrain, J. G. Neduvélil, S. R. Fletcher, R. Baker, A. P. Watt, A. E. Fletcher, S. B. Freedman, J. A. Kemp, G. R. Marshall, S. Patel, A. J. Smith and V. G. Matassa, *J. Med. Chem.*, 1994, **37**, 719–721.

- 47 M. B. van Niel, S. B. Freedman, V. G. Matassa, S. Patel, R. R. Pengilley and A. J. Smith, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1421–1426.
- 48 A. Walser, T. Flynn, C. Mason, H. Crowley, C. Maresca, B. Yaremko and M. O'Donnell, *J. Med. Chem.*, 1991, **34**, 1209–1221.
- 49 J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 2–24.
- 50 E. M. Hadac, E. S. Dawson, J. W. Darrow, E. E. Sugg, T. P. Lybrand and L. J. Miller, *J. Med. Chem.*, 2006, **49**, 850–863.
- 51 F. I. Carroll and W. A. Carlezon, *J. Med. Chem.*, 2013, **56**, 2178–2195.
- 52 B. Evans, A. Pipe, L. Clark and M. Banks, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1297–1300.
- 53 P. G. Wyatt, M. J. Allen, J. Chilcott, G. Hickin, N. D. Miller and P. M. Woollard, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1301–1305.
- 54 M. J. Fisher, B. Gunn, C. S. Harms, A. D. Kline, J. T. Mullaney, A. Nunes, R. M. Scarborough, A. E. Arfsten, M. A. Skelton, S. L. Um, B. G. Utterback and J. A. Jakubowski, *J. Med. Chem.*, 1997, **40**, 2085–2101.
- 55 R. S. McDowell, B. K. Blackburn, T. R. Gadek, T. Rawson, M. E. Reynolds, K. D. Robarge, T. C. Somers, M. Tischler, L. R. McGee, E. D. Thorsett, R. R. Webb and M. C. Venuti, *J. Am. Chem. Soc.*, 1994, **116**, 5077–5083.
- 56 R. M. Scarborough and D. D. Gretler, *J. Med. Chem.*, 2000, **43**, 3453–3473.
- 57 S. Ballet, D. Feytens, K. Buysse, N. N. Chung, C. Lemieux, S. Tumati, A. Keresztes, J. Van Duppen, J. Lai, E. Varga, F. Porreca, P. W. Schiller, J. Vanden Broeck and D. Tourwé, *J. Med. Chem.*, 2011, **54**, 2467–2476.
- 58 T. W. Ku, F. E. Ali, L. S. Barton, J. W. Bean, W. E. Bondinell, J. L. Burgess, J. F. Callahan, R. R. Calvo, L. Chen, D. S. Eggleston, J. G. Gleason, W. F. Huffman, S. M. Hwang, D. R. Jakas, C. B. Karash, R. M. Keenan, K. D. Kopple, W. H. Miller, K. A. Newlander, A. Nichols, M. F. Parker, C. E. Peishoff, J. M. Samanen, I. Uzinskas and J. W. Venslavsky, *J. Am. Chem. Soc.*, 1993, **115**, 8861–8862.
- 59 M. H. Bolli, J. Marfurt, C. Grisostomi, C. Boss, C. Binkert, P. Hess, A. Treiber, E. Thorin, K. Morrison, S. Buchmann, D. Bur, H. Ramuz, M. Clozel, W. Fischli and T. Weller, *J. Med. Chem.*, 2004, **47**, 2776–2795.
- 60 G. Boerrigter and J. C. Burnett, *Coron. Artery Dis.*, 2003, **14**, 495–500.
- 61 G. Remuzzi, N. Perico and A. Benigni, *Nat. Rev. Drug Discov.*, 2002, **1**, 986–1001.
- 62 J. G. Filep, *Drugs of Today*, 1995, **31**, 155–171.
- 63 D. R. Armour, N. M. Aston, K. M. L. Morriss, M. S. Congreve, A. B. Hawcock,

- D. Marquess, J. E. Mordaunt, S. A. Richards and P. Ward, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2037–2042.
- 64 F. Elijevovich and C. L. Laffer, *J. Hum. Hypertens.*, 2002, **16**, 459–467.
- 65 G. N. Prado, L. Taylor, X. Zhou, D. Ricupero, D. F. Mierke and P. Polgar, *J. Cell. Physiol.*, 2002, **193**, 275–286.
- 66 M. R. Wood, J. J. Kim, W. Han, B. D. Dorsey, C. F. Homnick, R. M. DiPardo, S. D. Kuduk, T. MacNeil, K. L. Murphy, E. V. Lis, R. W. Ransom, G. L. Stump, J. J. Lynch, S. S. O'Malley, P. J. Miller, T.-B. Chen, C. M. Harrell, R. S. L. Chang, P. Sandhu, J. D. Ellis, P. J. Bondiskey, D. J. Pettibone, R. M. Freidinger and M. G. Bock, *J. Med. Chem.*, 2003, **46**, 1803–1806.
- 67 M. Amblard, I. Daffix, G. Bergé, M. Calmès, P. Dodey, D. Pruneau, J. L. Paquet, J. M. Luccarini, P. Bélichard and J. Martinez, *J. Med. Chem.*, 1999, **42**, 4193–4201.
- 68 E. K. Dziadulewicz, M. C. Brown, A. R. Dunstan, W. Lee, N. B. Said and P. J. Garratt, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 463–468.
- 69 T. W. Ku, W. H. Miller, W. E. Bondinell, K. F. Erhard, R. M. Keenan, A. J. Nichols, C. E. Peishoff, J. M. Samanen, A. S. Wong and W. F. Huffman, *J. Med. Chem.*, 1995, **38**, 9–12.
- 70 W. H. Miller, D. P. Alberts, P. K. Bhatnagar, W. E. Bondinell, J. F. Callahan, R. R. Calvo, R. D. Cousins, K. F. Erhard, D. A. Heerding, R. M. Keenan, C. Kwon, P. J. Manley, K. A. Newlander, S. T. Ross, J. M. Samanen, I. N. Uzinskas, J. W. Venslavsky, C. C. K. Yuan, R. C. Haltiwanger, M. Gowen, S. M. Hwang, I. E. James, M. W. Lark, D. J. Rieman, G. B. Stroup, L. M. Azzarano, K. L. Salyers, B. R. Smith, K. W. Ward, K. O. Johanson and W. F. Huffman, *J. Med. Chem.*, 2000, **43**, 22–26.
- 71 R. M. Keenan, J. F. Callahan, J. M. Samanen, W. E. Bondinell, R. R. Calvo, L. Chen, C. DeBrosse, D. S. Eggleston, R. C. Haltiwanger, S. M. Hwang, D. R. Jakas, T. W. Ku, W. H. Miller, K. A. Newlander, A. Nichols, M. F. Parker, L. S. Southhall, I. Uzinskas, J. A. Vasko-Moser, J. W. Venslavsky, A. S. Wong and W. F. Huffman, *J. Med. Chem.*, 1999, **42**, 545–559.
- 72 H. G. Selnick, N. J. Liverton, J. J. Baldwin, J. W. Butcher, D. A. Claremon, J. M. Elliott, R. M. Freidinger, S. A. King, B. E. Libby, C. J. McIntyre, D. A. Pribush, D. C. Remy, G. R. Smith, A. J. Tebben, N. K. Jurkiewicz, J. J. Lynch, J. J. Salata, M. C. Sanguinetti, P. K. S. Siegl, D. E. Slaughter and K. Vyas, *J. Med. Chem.*,

- 1997, **40**, 3865–3868.
- 73 J. Spencer, R. P. Rathnam, A. L. Harvey, C. J. Clements, R. L. Clark, M. P. Barrett, P. E. Wong, L. Male, S. J. Coles and S. P. MacKay, *Bioorg. Med. Chem.*, 2011, **19**, 1802–1815.
 - 74 M. Hata and G. R. Marshall, *J. Comput. Aided. Mol. Des.*, 2006, **20**, 321–331.
 - 75 I. S. Moreira, P. A. Fernandes and M. J. Ramos, *Proteins Struct. Funct. Genet.*, 2007, **68**, 803–812.
 - 76 T. M. Williams, C. a Stump, D. N. Nguyen, A. G. Quigley, I. M. Bell, S. N. Gallicchio, C. B. Zartman, B.-L. Wan, K. Della Penna, P. Kunapuli, S. a Kane, K. S. Koblan, S. D. Mosser, R. Z. Rutledge, C. Salvatore, J. F. Fay, J. P. Vacca and S. L. Graham, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2595–2598.
 - 77 V. Azzarito, K. Long, N. S. Murphy and A. J. Wilson, *Nat. Chem.*, 2013, **5**, 161–173.
 - 78 C. G. Cummings and A. D. Hamilton, *Tetrahedron*, 2013, **69**, 1663–1668.
 - 79 M. Peters, M. Trobe, H. Tan, R. Kleineweischede and R. Breinbauer, *Chem. Eur. J.*, 2013, **19**, 2442–2449.
 - 80 C. G. Cummings and A. D. Hamilton, *Curr. Opin. Chem. Biol.*, 2010, **14**, 341–346.
 - 81 M. D. Cummings, C. Schubert, D. J. Parks, R. R. Calvo, L. V. LaFrance, J. Lattanze, K. L. Milkiewicz and T. Lu, *Chem. Biol. Drug Des.*, 2006, **67**, 201–205.
 - 82 B. L. Grasberger, T. Lu, C. Schubert, D. J. Parks, T. E. Carver, H. K. Koblish, M. D. Cummings, L. V. LaFrance, K. L. Milkiewicz, R. R. Calvo, D. Maguire, J. Lattanze, C. F. Franks, S. Zhao, K. Ramachandren, G. R. Bylebyl, M. Zhang, C. L. Manthey, E. C. Petrella, M. W. Pantoliano, I. C. Deckman, J. C. Spurlino, A. C. Maroney, B. E. Tomczuk, C. J. Molloy and R. F. Bone, *J. Med. Chem.*, 2005, **48**, 909–912.
 - 83 E. Heard and R. A. Martienssen, *Cell*, 2014, **157**, 95–109.
 - 84 R. D. Kornberg and Y. Lorch, *Cell*, 1999, **98**, 285–294.
 - 85 V. G. Allfrey, R. Faulkner and A. E. Mirsky, *Proc. Natl. Acad. Sci.*, 1964, **51**, 786–794.
 - 86 A. J. Bannister and T. Kouzarides, *Cell Res.*, 2011, **21**, 381–395.
 - 87 S. B. Rothbart and B. D. Strahl, *Biochim. Biophys. Acta. Gene. Regul. Mech.*, 2014, **1839**, 627–643.
 - 88 D. E. Sterner and S. L. Berger, *Microbiol. Mol. Biol. Rev.*, 2000, **64**, 435–459.

- 89 G. D. Bowman and M. G. Poirier, *Chem. Rev.*, 2015, **115**, 2274–2295.
- 90 B. Barneda-Zahonero and M. Parra, *Mol. Oncol.*, 2012, **6**, 579–589.
- 91 P. Filippakopoulos, S. Picaud, M. Mangos, T. Keates, J. P. Lambert, D. Barsyte-Lovejoy, I. Felletar, R. Volkmer, S. Müller, T. Pawson, A. C. Gingras, C. H. Arrowsmith and S. Knapp, *Cell*, 2012, **149**, 214–231.
- 92 J. W. Tamkun, R. Deuring, M. P. Scott, M. Kissinger, A. M. Pattatucci, T. C. Kaufman and J. A. Kennison, *Cell*, 1992, **68**, 561–572.
- 93 C. Martin and Y. Zhang, *Nat. Rev. Mol. Cell Biol.*, 2005, **6**, 838–849.
- 94 S. Dambacher, M. Hahn and G. Schotta, *Heredity*, 2010, **105**, 24–37.
- 95 O. B. Cox, T. Krojer, P. Collins, O. Monteiro, R. Talon, A. Bradley, O. Fedorov, J. Amin, B. D. Marsden, J. Spencer, F. von Delft and P. E. Brennan, *Chem. Sci.*, 2016, **7**, 2322–2330.
- 96 S. Mujtaba, Y. He, L. Zeng, A. Farooq, J. E. Carlson, M. Ott, E. Verdin and M. M. Zhou, *Mol. Cell*, 2002, **9**, 575–586.
- 97 P. Filippakopoulos and S. Knapp, *Nat. Rev. Drug Discov.*, 2014, **13**, 337–356.
- 98 J. E. Bolden, M. J. Peart and R. W. Johnstone, *Nat. Rev. Drug Discov.*, 2006, **5**, 769–784.
- 99 A. G. Kazantsev and L. M. Thompson, *Nat. Rev. Drug Discov.*, 2008, **7**, 854–868.
- 100 C. French, *Nat. Rev. Cancer*, 2014, **14**, 149–150.
- 101 E. B. Stelow, *Head Neck Pathol.*, 2011, **5**, 31–35.
- 102 K. T. Thurn, S. Thomas, A. Moore and P. N. Munster, *Future Oncol.*, 2011, **7**, 263–283.
- 103 P. K. Mazur, A. Herner, S. S. Mello, M. Wirth, S. Hausmann, F. J. Sánchez-Rivera, S. M. Lofgren, T. Kuschma, S. A. Hahn, D. Vangala, M. Trajkovic-Arsic, A. Gupta, I. Heid, P. B. Noël, R. Braren, M. Erkan, J. Kleeff, B. Sipos, L. C. Sayles, M. Heikenwalder, E. Heßmann, V. Ellenrieder, I. Esposito, T. Jacks, J. E. Bradner, P. Khatrri, E. A. Sweet-Cordero, L. D. Attardi, R. M. Schmid, G. Schneider, J. Sage and J. T. Siveke, *Nat. Med.*, 2015, **21**, 1163–1171.
- 104 P. Filippakopoulos, J. Qi, S. Picaud, Y. Shen, W. B. Smith, O. Fedorov, E. M. Morse, T. Keates, T. T. Hickman, I. Felletar, M. Philpott, S. Munro, M. R. McKeown, Y. Wang, A. L. Christie, N. West, M. J. Cameron, B. Schwartz, T. D. Heightman, N. La Thangue, C. A. French, O. Wiest, A. L. Kung, S. Knapp and J. E. Bradner, *Nature*, 2010, **468**, 1067–1073.
- 105 E. Nicodeme, K. L. Jeffrey, U. Schaefer, S. Beinke, S. Dewell, C. Chung, R.

- Chandwani, I. Marazzi, P. Wilson, H. Coste, J. White, J. Kirilovsky, C. M. Rice, J. M. Lora, R. K. Prinjha, K. Lee and A. Tarakhovsky, *Nat.*, 2010, **468**, 1119–1123.
- 106 J. M. Yi and T. O. Kim, *Intest. Res.*, 2015, **13**, 112–121.
- 107 R. Kalla, A. Adams, E. Nimmo, N. Kennedy, N. Ventham, M. Vatn, J. Jahnsen, P. Ricanek, J. Halfvarson, M. Pierik, F. Gomollon, I. Gut, M. D 'amato and J. Satsangi, *Lancet*, 2017, **389**, 52-59.
- 108 J. E. Delmore, G. C. Issa, M. E. Lemieux, P. B. Rahl, J. Shi, H. M. Jacobs, E. Kastritis, T. Gilpatrick, R. M. Paranal, J. Qi, M. Chesi, A. C. Schinzel, M. R. McKeown, T. P. Heffernan, C. R. Vakoc, P. L. Bergsagel, I. M. Ghobrial, P. G. Richardson, R. A. Young, W. C. Hahn, K. C. Anderson, A. L. Kung, J. E. Bradner and C. S. Mitsiades, *Cell*, 2011, **146**, 904–917.
- 109 M. L. McClelland, K. Mesh, E. Lorenzana, V. S. Chopra, E. Segal, C. Watanabe, B. Haley, O. Mayba, M. Yaylaoglu, F. Gnad and R. Firestein, *J. Clin. Invest.*, 2016, **126**, 639–652.
- 110 S. Shu, C. Y. Lin, H. H. He, R. M. Witwicki, D. P. Tabassum, J. M. Roberts, M. Janiszewska, S. J. Huh, Y. Liang, J. Ryan, E. Doherty, H. Mohammed, H. Guo, D. G. Stover, M. B. Ekram, G. Peluffo, J. Brown, C. D'Santos, I. E. Krop, D. Dillon, M. McKeown, C. Ott, J. Qi, M. Ni, P. K. Rao, M. Duarte, S. Y. Wu, C. M. Chiang, L. Anders, R. A. Young, E. P. Winer, A. Letai, W. T. Barry, J. S. Carroll, H. W. Long, M. Brown, X. S. Liu, C. A. Meyer, J. E. Bradner and K. Polyak, *Nature*, 2016, **529**, 413–417.
- 111 I. A. Asangani, V. L. Dommeti, X. Wang, R. Malik, M. Cieslik, R. Yang, J. Escara-Wilke, K. Wilder-Romans, S. Dhanireddy, C. Engelke, M. K. Iyer, X. Jing, Y. M. Wu, X. Cao, Z. S. Qin, S. Wang, F. Y. Feng and A. M. Chinnaiyan, *Nature*, 2014, **510**, 278–282.
- 112 M. Peifer, L. Fernández-Cuesta, M. L. Sos, J. George, D. Seidel, L. H. Kasper, D. Plenker, F. Leenders, R. Sun, T. Zander, R. Menon, M. Koker, I. Dahmen, C. Müller, V. Di Cerbo, H. U. Schildhaus, J. Altmüller, I. Baessmann, C. Becker, B. De Wilde, J. Vandesompele, D. Böhm, S. Ansén, F. Gabler, I. Wilkening, S. Heynck, J. M. Heuckmann, X. Lu, S. L. Carter, K. Cibulskis, S. Banerji, G. Getz, K. S. Park, D. Rauh, C. Grütter, M. Fischer, L. Pasqualucci, G. Wright, Z. Wainer, P. Russell, I. Petersen, Y. Chen, E. Stoelben, C. Ludwig, P. Schnabel, H. Hoffmann, T. Muley, M. Brockmann, W. Engel-Riedel, L. A. Muscarella, V. M.

- Fazio, H. Groen, W. Timens, H. Sietsma, E. Thunnissen, E. Smit, D. A. M. Heideman, P. J. F. Snijders, F. Cappuzzo, C. Ligorio, S. Damiani, J. Field, S. Solberg, O. T. Brustugun, M. Lund-Iversen, J. Sanger, J. H. Clement, A. Soltermann, H. Moch, W. Weder, B. Solomon, J. C. Soria, P. Validire, B. Besse, E. Brambilla, C. Brambilla, S. Lantuejoul, P. Lorimier, P. M. Schneider, M. Hallek, W. Pao, M. Meyerson, J. Sage, J. Shendure, R. Schneider, R. Buttner, J. Wolf, P. Nurnberg, S. Perner, L. C. Heukamp, P. K. Brindle, S. Haas and R. K. Thomas, *Nat. Genet.*, 2012, **44**, 1104–1110.
- 113 Z. Cheng, Y. Gong, Y. Ma, K. Lu, X. Lu, L. A. Pierce, R. C. Thompson, S. Muller, S. Knapp and J. Wang, *Clin. Cancer Res.*, 2013, **19**, 1748–1759.
- 114 B. Chapuy, M. R. McKeown, C. Y. Lin, S. Monti, M. G. M. Roemer, J. Qi, P. B. Rahl, H. H. Sun, K. T. Yeda, J. G. Doench, E. Reichert, A. L. Kung, S. J. Rodig, R. A. Young, M. A. Shipp and J. E. Bradner, *Cancer Cell*, 2013, **24**, 777–790.
- 115 J. Zuber, J. Shi, E. Wang, A. R. Rappaport, H. Herrmann, E. A. Sison, D. Magoon, J. Qi, K. Blatt, M. Wunderlich, M. J. Taylor, C. Johns, A. Chicas, J. C. Mulloy, S. C. Kogan, P. Brown, P. Valent, J. E. Bradner, S. W. Lowe and C. R. Vakoc, *Nature*, 2011, **478**, 524–528.
- 116 C. Berenguer-Daize, L. Astorgues-Xerri, E. Odore, M. Cayol, E. Cvitkovic, K. Noel, M. Bekradda, S. MacKenzie, K. Rezai, F. Lokiec, M. E. Riveiro and L. Ouafik, *Int. J. Cancer*, 2016, **139**, 2047–2055.
- 117 M. D. Sanna, L. Guandalini, M. N. Romanelli and N. Galeotti, *Pharmacol. Biochem. Behav.*, 2017, **160**, 70–75.
- 118 C. Wong, S. V. Laddha, L. Tang, E. Vosburgh, A. J. Levine, E. Normant, P. Sandy, C. R. Harris, C. S. Chan and E. Y. Xu, *Cell Death Dis.*, 2014, **5**, 1–14.
- 119 P. A. Marks, *Oncogene*, 2007, **26**, 1351–1356.
- 120 S. Yamamoto, K. Tanaka, R. Sakimura, T. Okada, T. Nakamura, Y. Li, M. Takasaki, Y. Nakabeppu and Y. Iwamoto, *Anticancer Res.*, 2008, **28**, 1585–1591.
- 121 A. Grabarska, J. J. Luszczki, E. Nowosadzka, E. Gumbarewicz, W. Jeleniewicz, M. Dmoszynska-Graniczka, K. Kowalczuk, K. Kupisz, K. Polberg and A. Stepulak, *J. Cancer*, 2017, **8**, 19–28.
- 122 R. L. Piekarz, R. Frye, M. Turner, J. J. Wright, S. L. Allen, M. H. Kirschbaum, J. Zain, H. M. Prince, J. P. Leonard, L. J. Geskin, C. Reeder, D. Joske, W. D. Figg, E. R. Gardner, S. M. Steinberg, E. S. Jaffe, M. Stetler-Stevenson, S. Lade, A. T. Fojo and S. E. Bates, *J. Clin. Oncol.*, 2009, **27**, 5410–5417.

- 123 H. M. Prince and M. Dickinson, *Clin. Cancer Res.*, 2012, **18**, 3509–3515.
- 124 P. Guan and H. Fang, *Drug Discov. Ther.*, 2010, **4**, 388–391.
- 125 M. Kim, L. A. Thompson, S. D. Wenger and C. L. O'Bryant, *Ann. Pharmacother.*, 2012, **46**, 1340–1348.
- 126 A. Sawas, D. Radeski and O. A. O'Connor, *Ther. Adv. Hematol.*, 2015, **6**, 202–8.
- 127 H. Z. Lee, V. E. Kwitkowski, P. L. Del Valle, M. S. Ricci, H. Saber, B. A. Habtemariam, J. Bullock, E. Bloomquist, Y. L. Shen, X.-H. Chen, J. Brown, N. Mehrotra, S. Dorff, R. Charlab, R. C. Kane, E. Kaminskas, R. Justice, A. T. Farrell and R. Pazdur, *Clin cancer res*, 2015, **21**, 2666–2670.
- 128 P. Campbell and C. M. Thomas, *J. Oncol. Pharm. Pract.*, 2017, **23**, 143–147.
- 129 G. J. KP, *Drugs*, 2015, **75**, 695–704.
- 130 M. A. Gertz, *Lancet Haematol.*, 2016, **3**, 552–553.
- 131 I. V. Gregoret, Y. M. Lee and H. V. Goodson, *J. Mol. Biol.*, 2004, **338**, 17–31.
- 132 W. S. Xu, R. B. Parmigiani and P. A. Marks, *Oncogene*, 2007, **26**, 5541–5552.
- 133 D. R. Reddy, F. Ballante, N. J. Zhou and G. R. Marshall, *Eur. J. Med. Chem.*, 2017, **127**, 531–553.
- 134 L. Loudni, J. Roche, V. Potiron, J. Clarhaut, C. Bachmann, J. P. Gesson and I. Tranoy-Opalinski, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4819–4823.
- 135 L. W. Mohamed and M. F. El-Yamany, *Arch. Pharm. Res.*, 2012, **35**, 1369–1377.
- 136 R. C. Sheppard and B. J. Williams, *Int. J. Pept. Protein Res.*, 1982, **20**, 451–454.
- 137 F. ALBERICIO and G. BARANY, *Int. J. Pept. Protein Res.*, 1987, **30**, 206–216.
- 138 L. A. Carpino, D. Sadat-Aalaei, H. G. Chao and R. H. DeSelms, *J. Am. Chem. Soc.*, 1990, **112**, 9651–9652.
- 139 S. Y. Han and Y. A. Kim, *Tetrahedron*, 2004, **60**, 2447–2467.
- 140 R. Behrendt, P. White and J. Offer, *J. Pept. Sci.*, 2016, **22**, 4–27.
- 141 B. A. Bunin, M. J. Plunkett and J. A. Ellman, *Proc. Natl. Acad. Sci.*, 1994, **91**, 4708–4712.
- 142 B. A. Bunin and J. A. Ellman, *J. Am. Chem. Soc.*, 1992, **114**, 10997–10998.
- 143 J. A. Ellman, *Acc. Chem. Res.*, 1996, **29**, 132–143.
- 144 M. J. Plunkett and J. A. Ellman, *J. Am. Chem. Soc.*, 1995, **117**, 3306–3307.
- 145 Y. Huang, K. Khoury, T. Chanas and A. Dömling, *Org. Lett.*, 2012, **14**, 5916–5919.
- 146 M. Saeedi, M. Mahdavi, A. Foroumadi and A. Shafiee, *Tetrahedron*, 2013, **69**, 3506–3510.

- 147 D. Mingji, *Tetrahedron*, 2006, **27**, 1–26.
- 148 Q. Tang, C. Liu, C. Zhong and J. Ding, *Mol. Plant*, 2015, **8**, 1557–1559.
- 149 J. a Stafford, G. J. Pacofsky, R. F. Cox, J. R. Cowan, G. F. Dorsey, S. S. Gonzales, D. K. Jung, G. W. Koszalka, M. S. McIntyre, J. H. Tidwell, R. P. Wiard and P. L. Feldman, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3215–3218.
- 150 J. Spencer, D. P. Sharratt, J. Dupont, A. L. Monteiro, V. I. Reis, M. P. Stracke, F. Rominger and I. M. McDonald, *Organometallics*, 2005, **24**, 5665–5672.
- 151 J. Spencer, B. Z. Chowdhry, A. I. Mallet, R. P. Rathnam, T. Adatia, A. Bashall and F. Rominger, *Tetrahedron*, 2008, **64**, 6082–6089.
- 152 A. J. Close, P. Kemmitt, M. K. Emmerson and J. Spencer, *Tetrahedron*, 2014, **70**, 9125–9131.
- 153 C. O. Kappe, *Angew. Chem. Int. Ed.*, 2004, **43**, 6250–6284.
- 154 M. J. Gronnow, R. J. White, J. H. Clark and D. J. Macquarrie, *Org. Process Res. Dev.*, 2005, **11**, 293–293.
- 155 J. Spencer, C. B. Baltus, H. Patel, N. J. Press, S. K. Callear, L. Male and S. J. Coles, *ACS Comb. Sci.*, 2011, **13**, 24–31.
- 156 C. O. Kappe, B. Pieber and D. Dallinger, *Angew. Chem. Int. Ed.*, 2013, **52**, 1088–1094.
- 157 J. S. Schanche, *Mol. Divers.*, 2003, **7**, 291–298.

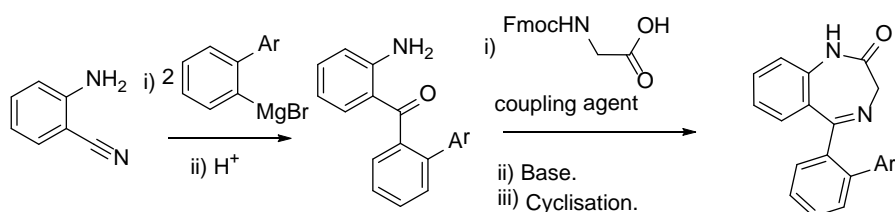
Chapter 2

Late Stage C H Activation of a Privileged Scaffold; Synthesis of a Library of Benzodiazepines

2.1 Introduction

The need for efficiency in rapidly producing a library of closely related analogues cannot be understated in drug discovery where natural product derivatives or complex molecules, often synthesized by multistep reactions, are fine-tuned to respond to inadequacies in terms of their biological activity, selectivity, pharmacokinetics and undesirable toxicity. The ability to add functionality to a bioactive core at the final or penultimate synthetic step to enable SAR (structure activity relationship) studies can drive efficiency and speed up hit-to-lead and lead optimization strategies.^{1–18}

We have a longstanding interest in benzodiazepines, which represent an important class of privileged heterocycles.^{19–30} Typical routes for the introduction of different R groups at the 5-position are inefficient since such reactions are early in the synthetic sequence and this is followed by repetitive coupling/cyclisation chemistries (Scheme 2.1).

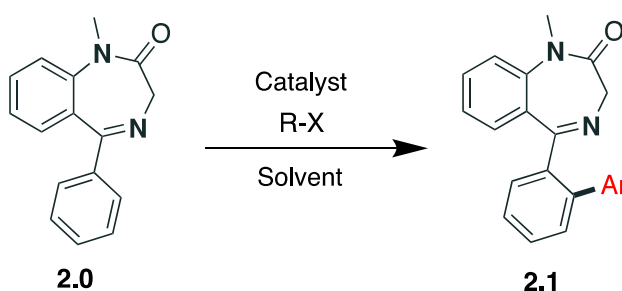


Scheme 2.1: A classical route to a 5-(2-arylphenyl)-2,3-dihydro-1H-1,4-benzodiazepin-2-one

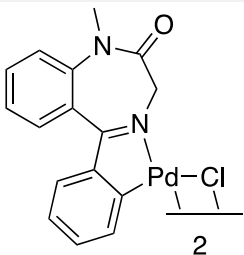
2.2 Results and Discussion

Our approach sought to vary the 5-substituent via a late-stage C-H activation; in essence, a benzodiazepine building block could be synthesized, once, on a large scale using the coupling/cyclisation chemistry discussed above, then functionalised by introducing the new functional groups at the last step, adding atom and step economy³¹ to the library generation process. Our test case was the chelation-assisted C-H activation of the valium (diazepam)-like benzodiazepine **2.0** using palladacycle chemistry to afford **2.1** (Table 2.1).^{32–37} Notably, Cintrat *et al.* showed ortho-halogenation³⁴ of the aryl group can be achieved under similar conditions, opening up the possibility of carrying out complementary Pd-mediated couplings. A rapid screen of conditions showed that this was indeed possible and that the best conversion, by ¹H NMR, involved acetic acid as solvent, microwave conditions,^{38,39} and employed 5 mol% Pd(OAc)₂ as catalyst and Ph₂IBF₄^{40–44} as the arylating agent (Entry 2). The use of a mesityl-aryl iodonium salt gave similar promising results (entry 4) and will be exploited further on (*vide infra*). Further iterations (Table 2), including the use of classical, thermal conditions, lower Pd loadings, additives such as silver salts,^{45,46} led to no or little improvement, although higher concentrations of reagents led to slightly improved conversions (Entry 9, Table 2).

Table 2. 1: Optimization of C-H Activation^a



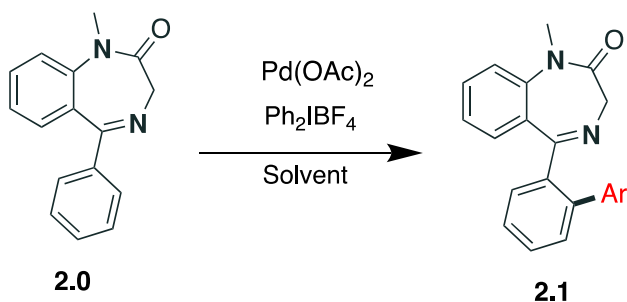
Entry	R-X (equiv.)	Catalyst (mol%)	Time (h)	Temp. (°C)	Conversion by NMR/LC-MS (%)	Solvent
1	Ph ₂ IBF ₄ (1.5)	-	1.5	125	0	AcOH

2	Ph ₂ IBF ₄ (1.5)	Pd(OAc) ₂ (5)	1.5	125	55	AcOH
3	Ph ₂ IBF ₄ (1.5)	Pd(OAc) ₂ (5)	1.5	125	5	EtOAc
4	[Mes-I-Ar]OTf (1.5)	Pd(OAc) ₂ (5)	1.5	125	50	AcOH
5	PhBr (1.5)	Pd(OAc) ₂ (5)	1	125	0	AcOH
6	Ph ₂ IBF ₄ (1.5)	 2	1.5	125	22	AcOH
7	Ph ₂ IBF ₄ (2.5)	(MeCN) ₂ PdCl ₂ (10)	1.5	125	0	AcOH
8	Ph ₂ IBF ₄ (1.5)	(MeCN) ₂ PdCl ₂ (10)	1.5	125	0	DCE
9	Ph ₂ IBF ₄ (1.5)	Pd(OAc) ₂ (2.5)	1.5	125	0	AcOH

^a All reactions were conducted in a CEM Explorer microwave unless stated otherwise. DCE = 1,2-dichloroethane; EtOAc = ethyl acetate.

^b Conventional heating.

Table 2.2: Further optimisation studies^a



Entry	Ph ₂ IBF ₄ (equiv.)	Pd(OAc) ₂ (mol%)	Time (h)	Temp. (°C)	Conversion by NMR (%)	AcOH (mL)
1 ^b	1.5	5	64	100	44	5

2 ^c	1.5	100	1.5	125	0	5
3	1.5	5	0.15+0.5	150+120	28	5
4	1.5	10	2	130	47	5
5	2.5	10	1	125	51	5
6	1.5	10	1	125	48	5
7	1.5	5	1.25	125	54	5
8	1.5	10	1.5	125	55	5
9	1.5	5	1	125	58	2.5
10	1.5	5	1	125	33	2.5
11 ^d	1.5	5	1	125	20	2.5
12 ^f	1.5	5	1	125	16	2.5
13 ^g	1.5	5	1	125	54	2.5
14 ^h	1.5	5	1	125	30	2.5

^a All reactions were conducted in a CEM Explorer microwave unless stated otherwise.

^b Conventional heating.

^c Analysis of the crude mixture, after PPh₃ treatment, showed evidence that the palladacycle was formed.

^d Ag₂O added (1.5 equiv.)

^e Ag₂O added (1.5 equiv. at 100 °C)

^f AgOAc added (1.5 equiv. at 100 °C)

^g AcOH degassed, reaction under N₂.

^h AcOH dry and degassed, reaction under N₂.

Using our “optimised” approach we synthesised a range of benzodiazepines via this last-stage C-H activation protocol. Critically, we were able to confirm the C-H activation had occurred in the ortho-position as anticipated from a chelation controlled process by crystal-structure determinations of a number of products (*vide infra*)⁴⁷ (Figure 2.1). We synthesized a series of fluorinated aromatics 2 due to their advantageous role of fluorine in medicinal chemistry.⁴⁸

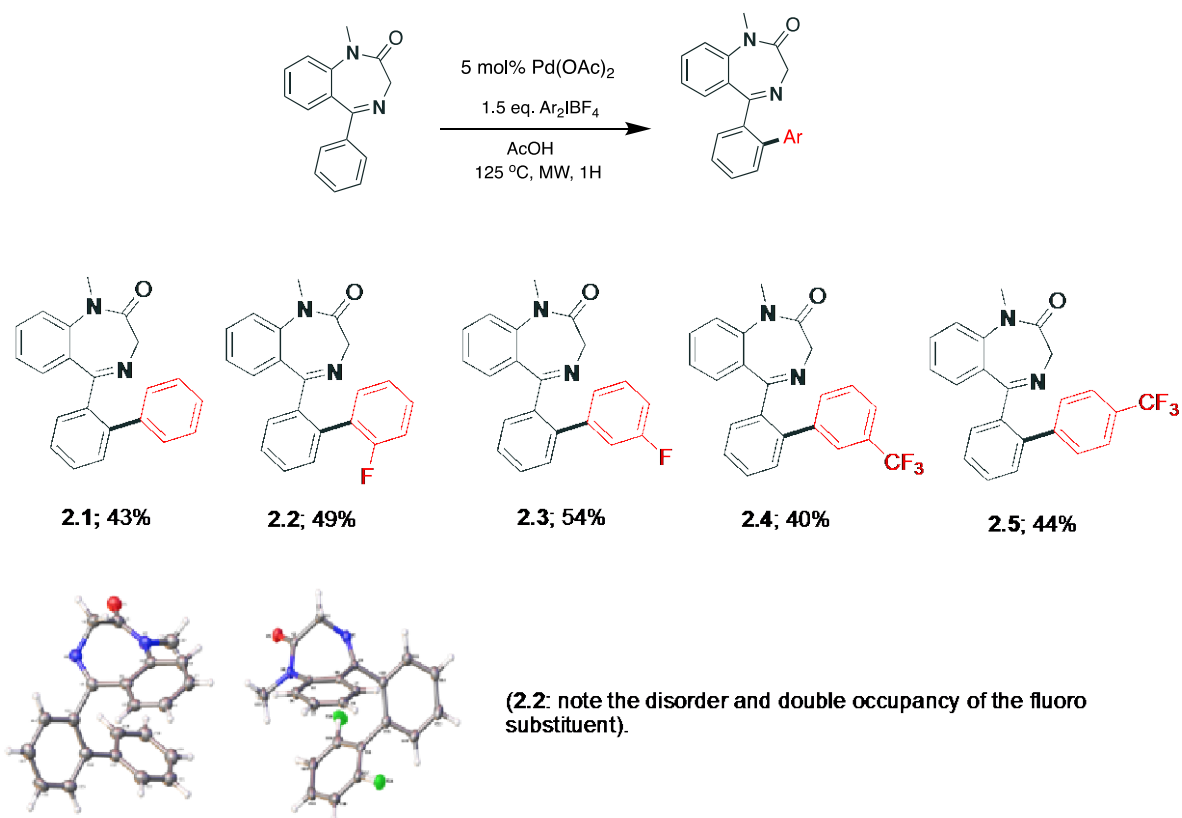
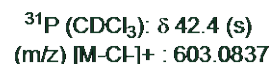


Figure 2.1: Ortho-arylated BZDs

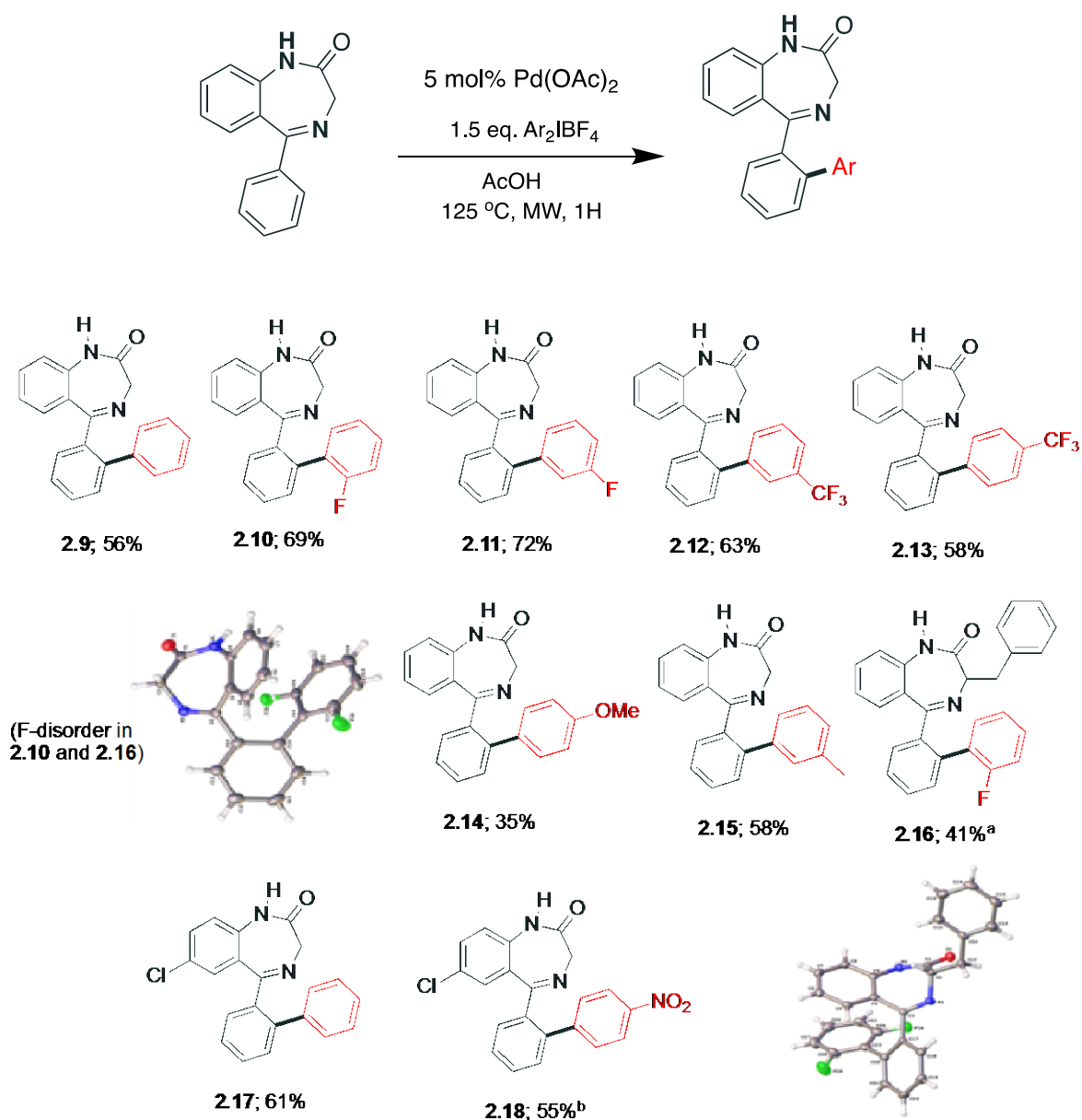
At this stage, we were still somewhat dissatisfied with this approach since we were confined to a *N*1-methyl substituent in the final product. A broader diversity would be enabled by having a *N*-protected or free amide group, enabling further diversification after the arylation reaction. To test the more attractive latter hypothesis, preliminary studies on the C-H activation process were carried out (Scheme 2.2) and established that:

- i) Stoichiometric chelation-assisted C-H activation is indeed possible on the unsubstituted N-H amide since the palladacycle **3** can be isolated.
- ii) An attempted interception of the palladacycle intermediate, by a Pd-catalyzed H/D exchange,^{49–52} did not lead to the expected product **1c**. Instead, this reaction, furnished uniquely the D₂-methylene compound **1d**, which could *also be accomplished in the absence of the metal catalyst* by merely stirring in deuterated acetic acid in the microwave, similar to previous findings on H/D exchange.^{53,54}



Scheme 2.2: Deuteration and palladation reactions of 2.0

Next, we produced a library of benzodiazepines lacking a N1-substituent (Figure 2.2). Of note, we were also able to produce arylated nordazepam⁵⁵ derivatives; nordazepam was quickly made by an adaptation of a microwave protocol.⁵⁶ Yields, in general, were superior to those for their N-methylated analogues, mainly with electron-poor arenes, whereas the electron-rich **2.14** and **2.15** were made in moderate yield (note: the 2-tolyl derivative of **2.15** did not form, possibly due to steric effects). We were pleasantly surprised to be able to obtain the hindered **2.16**, albeit under more forcing microwave conditions. Analogue **2.18** was made from a mesityl-containing arylodonium salt.

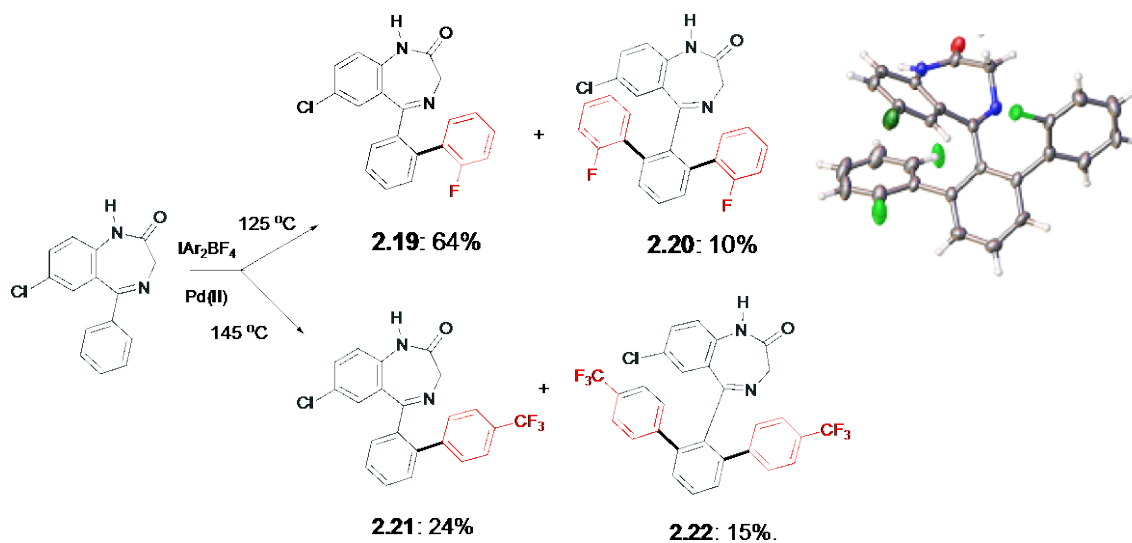


^a 150 °C reaction temperature

^b From its corresponding (4-nitrophenyl(2,4,5-trimethylphenyl)iodonium salt

Figure 2.2: C-H arylation of 1N-H benzodiazepines

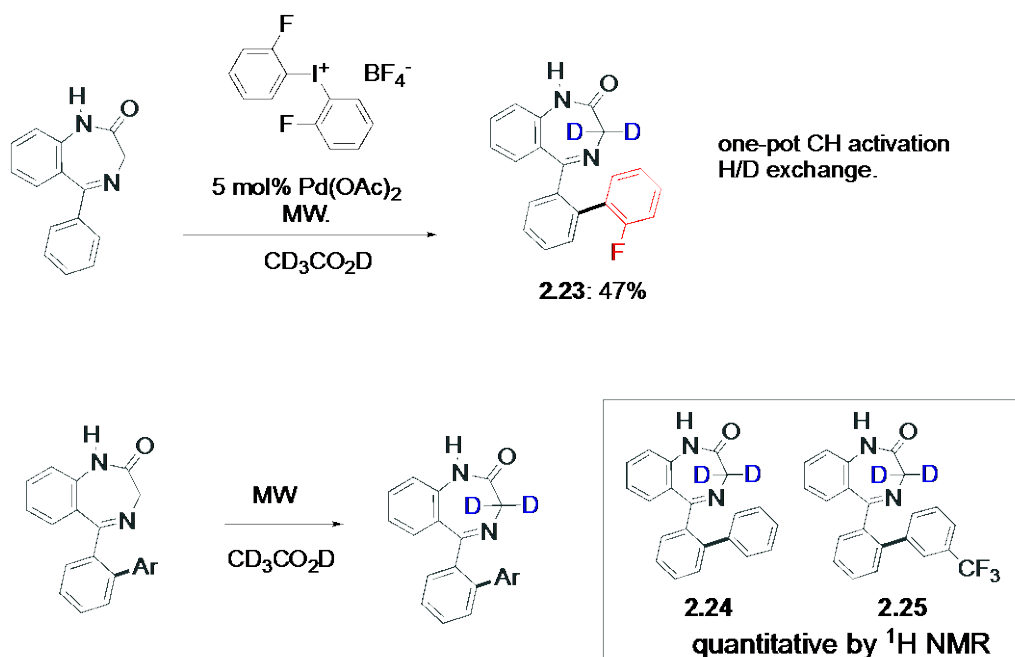
Products were separated initially using a mass-triggered LC-MS protocol⁵⁷ but we found that a reversed-phase LC-MS method was equally useful and we were also able to recover traces of unreacted starting material. Moreover, diarylated products were often observed in the crude reaction mixtures and, in some cases, were isolated (Scheme 2.3, e.g. **2.20**, **2.22**). The yields of **2.21** and **2.22** were rather low, even when using a higher temperature.



Scheme 2.3: Nordazepam mono- and diarylations

Following our earlier studies (Scheme 2.2) we prepared a small number of deuterated derivatives **2.23** – **2.25** (Scheme 2.4). Compound **2.23**, the deuterated analogue of **2.10**, was prepared by a one-pot dual C-H activation/H-D exchange by simply carrying out the catalytic arylation protocol in $\text{CD}_3\text{CO}_2\text{D}$ whereas **2.24**, **2.25** were simply prepared by stirring the arylated precursors in $\text{CD}_3\text{CO}_2\text{D}$ in a microwave.

Deuterated benzodiazepine products were easily characterized, e.g. by ^2H NMR (note: ND tends to revert to NH when the samples are concentrated in air).



Scheme 2.4: Synthesis of deuterated elaborated benzodiazepines

A further illustration of the diversity achievable is that the resulting elaborated nordazepam derivatives can be *N*-alkylated to afford substituted diazepam and pinazepam analogues (Figure 2.3).

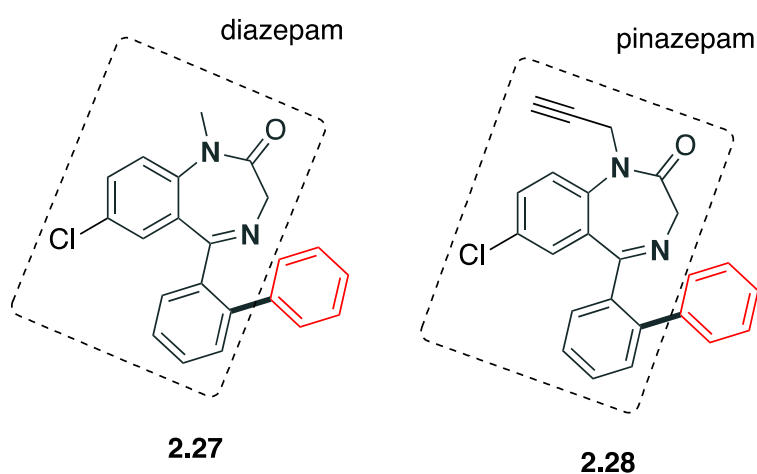


Figure 2.3: Ortho-arylated pharmaceuticals

2.3 Conclusion

In summary, we have synthesized a library of benzodiazepines via a late stage C-H activation reaction. Future work may aim to address the drug-likeness of the products by e.g. lowering their clogP, testing their biological activity, as well as applying this chemistry to other systems related to benzodiazepines such as benzotriazepines.⁵⁸⁻⁶² CCDC-1422838 – CCDC-1422844 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.4 Experimental details for Chapter 2

All commercially purchased materials and solvents were used without further purification unless specified otherwise. NMR spectra were recorded on a Varian VNMRs 500 (¹H 500 MHz, ¹³C 126 MHz) and VNMRs 400 (¹⁹F 376 MHz, ²H 61 MHz and ³¹P 162 MHz) spectrometer and prepared in deuterated solvents such as CDCl₃ and DMSO-d₆. ¹H and ¹³C chemical shifts were recorded in parts per million (ppm). Multiplicity of ¹H-NMR peaks are indicated by s – singlet, d – doublet, dd – doublets of doublets, t – triplet, pt – pseudo triplet, q – quartet, m – multiplet and coupling constants are given in Hertz (Hz). Electrospray ionisation – high resolution mass spectra (ESI-HRMS) were obtained using a Bruker Daltonics Apex III where Apollo ESI was used as the ESI source. All analyses were conducted by Dr A. K. Abdul-Sada. The molecular ion peaks [M]⁺ were recorded in mass to charge (m/z) ratio.

LC-MS spectra were acquired using Shimadzu LC-MS 2020, on a Gemini 5 m C18 110 Å. column. All X-ray analyses were performed at the UK National Crystallography Services, Southampton. All elemental analyses were carried out at the Elemental Analysis Service, London Metropolitan University. Purifications were performed by flash chromatography on silica gel columns or C18 columns using a Combi flash RF 75 PSI, ISCO unit.

2.4.1 1-Methyl-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2.1)

1-Methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.15 g, 0.60 mmol), diphenyliodonium tetrafluoroborate (0.33 g, 0.90 mmol) and palladium (II) acetate (6.0 mg, 5 mol %) were combined in glacial acetic acid (4 mL) and stirred for 1h at 125 °C in the microwave. Thereafter the cooled reaction mixture was filtered over celite, washed with dichloromethane (DCM, 10 mL) and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL), washed with saturated sodium bicarbonate and the organic layer was collected using a (hydrophobic frit) phase separator. The solution was concentrated under reduced pressure to yield an orange product. The crude material was purified by flash chromatography (30 g C18, acetonitrile: water, 30 % to 90 %) and the final product was obtained (0.083 g, 43 %) as a white powder.

¹H-NMR (500 MHz) CDCl₃: δ = 7.78 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.29 (dd, *J* = 6.7, 1.9 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.11 – 7.20 (m, 3H), 6.93 (d, *J* = 6.4 Hz, 2H), 6.91 – 6.85 (m, 3H), 4.83 (d, *J* = 11.0 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 3.15 (s, 3H).
¹³C-NMR (126 MHz) CDCl₃: δ = 173.0, 169.5, 139.5, 143.0, 142.1, 140.8, 138.6, 131.2, 130.5, 130.1, 130.0, 129.1, 128.7 (2C), 127.7 (2C), 127.5, 126.4, 123.3, 120.0, 56.3, 34.9.

HRMS-ESI (*m/z*) Calculated for C₂₂H₁₈N₂O [*+H*]⁺: 327.1497, found: 327.1492.
 Elemental Analysis: Calculated for C₂₂H₁₈N₂O (%): C, 80.96, H, 5.56, N, 8.58; found: C, 80.69, H, 5.32, N, 8.54.

2.4.2 1-Methyl-5-(2'-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2.2)

This was synthesised on a 0.31 mmol scale by the same procedure as 2.1 and bis(2-fluorophenyl)iodonium tetrafluoroborate (0.18 g, 0.49 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained (0.052 g, 49 %) as a white powder.

¹H-NMR (500 MHz) CDCl₃: δ = 7.78 (dd, *J* = 5.8, 3.4 Hz, 1H), 7.52 (dd, *J* = 5.8, 3.4 Hz, 2H), 7.31 (dd, *J* = 5.5 Hz, 3.5 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.11 – 7.05 (m, 1H), 6.98 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.96-6.92 (m, 2H), 6.91 (d, *J* = 3.1 Hz, 1H), 6.89 (d, *J* = 2.2 Hz,

1H), 6.72 (pt, $J = 9.0$ Hz, 1H), 4.78 (d, $J = 10.8$ Hz, 1H), 3.68 (d, $J = 10.8$ Hz, 1H), 3.14 (s, 3H).

^{13}C -NMR (126 MHz) CDCl_3 : $\delta = 171.7, 170.3, 158.9$ (d, $^1J_{\text{FC}} = 247.3$ Hz), 142.8, 139.7, 135.6, 131.5 (d, $^3J_{\text{FC}} = 3.1$ Hz), 130.8, 130.4, 129.9, 129.4, 129.1, 128.6 (d, $^3J_{\text{FC}} = 8.0$ Hz), 128.5 (d, $^2J_{\text{FC}} = 16.1$ Hz), 128.4, 128.1, 123.4, 123.3 (d, $^4J_{\text{FC}} = 3.8$ Hz), 119.9, 115.0 (d, $^2J_{\text{FC}} = 22.3$ Hz), 56.6, 35.0. ^{19}F -NMR (376 MHz) CDCl_3 : $\delta = -115.1$ (1F).

HRMS-ESI (m/z) Calculated for $\text{C}_{22}\text{H}_{17}\text{FN}_2\text{O}$ $[\text{+H}]^+$: 345.1398, found: 345.1390. Elemental Analysis: Calculated for $\text{C}_{22}\text{H}_{17}\text{FN}_2\text{O}$ (%): C, 76.73, H, 4.98, N, 8.13; found: C, 76.59, H, 4.82, N, 8.26.

2.4.3 1-Methyl-5-(3'-fluorobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.3**)

The same procedure as **2.1** was used but bis(3-fluorophenyl)iodonium tetrafluoroborate (0.18 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained (0.111 g, 54 %) as a white powder.

^1H -NMR (500 MHz) DMSO-d_6 : δ 7.70 (d, $J = 7.4$ Hz, 1H), 7.64 – 7.55 (m, 2H), 7.35 (d, $J_{\text{FH}} = 7.4$ Hz, 2H), 7.18 – 7.13 (m, 2H), 6.96 (pt, $J = 7.8$ Hz, 2H), 6.74 (d, $J = 7.8$ Hz, 1H), 6.71 (d, $J_{\text{FH}} = 7.7$ Hz, 1H), 6.67 (d, $J = 10.0$ Hz, 1H), 4.55 (d, $J = 11.0$ Hz, 1H), 3.69 (d, $J = 11.0$ Hz, 1H), 3.10 (s, 3H).

^{13}C -NMR (126 MHz) DMSO-d_6 : $\delta = 172.3, 168.9, 162.1$ (d, $^1J_{\text{FC}} = 244.9$ Hz), 143.1 (d, $^3J_{\text{FC}} = 11.9$ Hz), 140.5, 138.6, 132.1, 131.1, 130.4, 130.4 (d, $^3J_{\text{FC}} = 4.3$ Hz), 130.3, 129.4, 129.1, 128.3, 125.0, 124.0, 121.1, 115.5 (d, $^2J_{\text{FC}} = 21.8$ Hz), 114.0 (d, $^2J_{\text{FC}} = 20.9$ Hz), 114.1, 56.6, 34.8. ^{19}F -NMR (376 MHz) DMSO-d_6 : $\delta = -113.4$ (1F).

HRMS-ESI (m/z) Calculated for $\text{C}_{22}\text{H}_{17}\text{FN}_2\text{O}$ $[\text{+H}]^+$: 345.1398, found: 345.1394. LCMS purity (UV) = 96 %, retention time (tR) 15.13 min.

2.4.4 1-Methyl-5-(3'-trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2.4**)

The same procedure as **2.1** was used but bis(3-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained (0.095 g, 40 %) as a white powder.

¹H-NMR (500 MHz) CDCl₃: δ = 7.79 – 7.74 (m, 1H), 7.57 – 7.53 (m, 2H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 7.16 – 7.14 (m, 1H), 6.94 – 6.85 (m, 3H), 4.81 (d, *J* = 10.9 Hz, 1H), 3.69 (d, *J* = 10.9 Hz, 1H), 3.10 (s, 3H).

¹³C-NMR (126 MHz) CDCl₃: δ = 172.0, 169.7, 142.8, 141.9, 140.6, 139.1, 132.3, 131.2, 130.4, 130.6, 130.0 (q, ²*J*_{FC} = 29.9 Hz), 129.9, 129.8, 129.1, 128.1, 127.9, 125.2 (q, ³*J*_{FC} = 3.2 Hz), 123.7 (q, ¹*J*_{FC} = 272.9 Hz), 123.4, 123.1 (q, ³*J*_{FC} = 3.8 Hz), 119.9, 56.7, 34.7.

¹⁹F-NMR (376 MHz) CDCl₃: δ = -63.3 (s, 3F).

HRMS-ESI (*m/z*) Calculated for C₂₃H₁₇F₃N₂O [*+H*]⁺: 395.1366, found: 395.1381. LCMS purity (UV) = 95 %, tR 18.14 min.

2.4.5 1-Methyl-5-(4'-trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2.5**)

The same procedure as **2.1** was used but bis(4-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained (0.104 g, 44 %) as a white powder.

¹H-NMR (500 MHz) DMSO-*d*₆: δ = 7.72 – 7.68 (m, 1H), 7.61-7.58 (m, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.28 (m, 2H), 7.12 – 7.05 (m, 3H), 6.97 – 6.90 (m, 1H), 6.74 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.54 (d, *J* = 10.9 Hz, 1H), 3.64 (d, *J* = 10.9 Hz, 1H), 3.04 (s, 3H).

¹³C-NMR (126 MHz) DMSO-*d*₆: δ = 171.6, 169.2, 145.0, 143.1, 140.3, 139.2, 131.8, 131.0, 130.4, 130.2, 129.7, 129.5 (2C), 128.9, 128.6, 127.6 (q, ²*J*_{FC} = 31.6 Hz), 125.1 (q, ³*J*_{FC} = 3.7 Hz, 2C), 124.6 (q, ¹*J*_{FC} = 272 Hz), 123.9, 120.8, 56.9, 34.7. ¹⁹F-NMR (376 MHz) CDCl₃: δ = -61.15 (s, 3F).

HRMS-ESI (m/z) Calculated for $C_{23}H_{17}F_3N_2O$ $[+H]^+$: 395.1366, found: 395.1374. Elemental Analysis: Calculated for $C_{23}H_{17}F_3N_2O$ (%): C, 70.04, H, 4.34, N, 7.10; found: C, 69.95, H, 4.38, N, 6.98.

2.4.6 Palladacycle (2.6)

5-Phenyl-1H-1,4-diazepin-2(3H)-one (0.20 g, 0.85 mmol) and sodium tetrachloropalladate (0.23 g, 0.78 mmol) were combined in ethanol (20 mL) for 48 hours at room temperature. The orange precipitate was filtered and washed with further ethanol (10 mL) and chloroform (10 mL). An orange solid powder was collected after drying in vacuo (0.25 g, 69 %). The product was too insoluble for NMR analysis. The product from above reaction (0.15 g, 0.33 mmol) and triphenylphosphine (0.08 g, 0.30 mmol) were combined in dichloromethane (10 mL) and stirred overnight. The resulting unwanted precipitate was filtered through celite and the filtrate was concentrated in vacuo. Hexane was added to the concentrated crude product to induce precipitation, filtered and dried under vacuum. The product was obtained (0.12 g, 63 %) as a yellow solid.

1H -NMR (500 MHz) $CDCl_3$: δ = 9.29 (s, 1H), 7.81 – 7.75 (m, 6H), 7.72 (d, J = 8.4 Hz, 2H), 7.59 (pt, J = 7.8 Hz, 1H), 7.44 – 7.41 (m, 3H), 7.39 – 7.34 (m, 5H), 7.30 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 7.7 Hz, 1H), 6.83 (pt, J = 7.3 Hz, 1H), 6.57 – 6.49 (m, 2H), 6.15 (d, J = 12.2 Hz, 1H), 3.81 (d, J = 12.2 Hz, 1H).

^{13}C -NMR (500 MHz) $CDCl_3$: δ = 182.3, 171.6, 159.1, 147.8, 138.6, 135.5 (2C), 135.4 (4C), 135.0 (2C), 132.5, 131.4, 131.2, 131.0, 130.9, 130.6 (2C), 130.4, 130.2, 128.0 (4C), 127.9 (2C), 124.3, 123.5, 123.4, 121.9, 53.9. ^{31}P -NMR (162 MHz) $CDCl_3$: δ = 42.4 (s, 1P).

HRMS-ESI (m/z) Calculated for $C_{33}H_{26}ClN_2OPPd$ $[-Cl]^+$: 603.0812, found: 603.0837. Elemental Analysis: Calculated for $C_{33}H_{26}ClN_2OPPd \cdot 0.9 CH_2Cl_2$ (%): C, 56.88, H, 3.91, N, 3.91; found: C, 56.69, H, 4.02, N, 3.84.

2.4.7 5-Phenyl-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2.9)

5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.14 g, 0.59 mmol), diphenyliodonium tetrafluoroborate (0.33 g, 0.90 mmol) and palladium (II) acetate (6.0 mg, 5 mol %) were combined in degassed glacial acetic acid (4 mL) and stirred for 1 h at 125 °C. Thereafter the cooled reaction mixture was filtered over celite, washed with DCM (10 mL) and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL), washed with saturated sodium bicarbonate and the organic layer was collected using a (hydrophobic frit) phase separator. The solution concentrated under reduced pressure to yield an orange product. The crude material was purified by flash chromatography (30 g C18, acetonitrile: water, 30 % to 90 %). Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.031 g, 0.13 mmol) and the final product was obtained (0.079 g, 56 %) as a white powder.

¹H-NMR (500 MHz) DMSO-*d*₆: δ = 10.33 (s, 1H), 7.57 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.34 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.12 – 7.04 (m, 3H), 6.95 – 6.90 (m, 2H), 6.79 (dd, *J* = 7.9, 6.4 Hz, 2H), 6.74 – 6.70 (m, 1H), 4.04 (s, 2H).

¹³C-NMR (126 MHz) DMSO-*d*₆: δ = 172.3, 169.7, 141.5, 140.5, 139.8, 139.2, 131.3, 130.9, 130.2, 130.1, 129.4, 128.6 (2C), 128.3, 128.0 (2C), 127.6, 127.1, 122.6, 120.7, 57.3.

HRMS-ESI (*m/z*) Calculated for C₂₁H₁₆N₂O [*+H*]⁺: 313.1335, found: 313.1336. Elemental Analysis: Calculated for C₂₁H₁₆N₂O (%): C, 80.75, H, 5.16, N, 8.97; found: C, 80.64, H, 5.06, N, 9.08.

2.4.8 5-(2'-Fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2.10)

The same method as **2.9** was used but bis(2-fluorophenyl)iodonium tetrafluoroborate (0.36 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.021 g, 0.09 mmol) and the final product was obtained (0.114 g, 69 %) as a white powder.

^1H -NMR (500 MHz) DMSO- d_6 : δ = 10.25 (s, 1H), 7.59 – 7.49 (m, 3H), 7.35 – 7.30 (m, 1H), 7.22 (ddd, J = 6.7, 2.0 Hz, $^3J_{\text{FH}}$ = 8.4 Hz, 1H), 7.16 – 7.10 (m, 1H), 6.97 – 6.87 (m, 3H), 6.86 – 6.85 (m, 2H), 6.83 (d, J = 8.2 Hz, 1H), 3.97 (s, 2H).

^{13}C -NMR (126 MHz) DMSO- d_6 : δ = 175.9, 174.6, 163.4 (d, $^1J_{\text{FC}}$ = 247.3 Hz), 145.3, 143.8, 140.3, 136.2 (d, $^4J_{\text{FC}}$ = 3.2 Hz), 136.1, 135.8, 135.4, 134.5, 134.4 (t, $^3J_{\text{FC}}$ = 4.1 Hz), 133.1, 132.9 (d, $^2J_{\text{FC}}$ = 15.6 Hz), 132.7, 128.9 (d, $^3J_{\text{FC}}$ = 3.5 Hz), 127.4, 125.5, 120.1, 120.0 (d, $^2J_{\text{FC}}$ = 22.1 Hz), 62.1. ^{19}F -NMR (376 MHz) DMSO- d_6 : δ = -113.4 (1F).

HRMS-ESI (m/z) Calculated for $\text{C}_{21}\text{H}_{15}\text{FN}_2\text{O}$ [$+\text{H}$] $^+$: 331.1241, found: 331.1232. Elemental Analysis: Calculated for $\text{C}_{21}\text{H}_{15}\text{FN}_2\text{O}$ (%): C, 76.35, H, 4.58, N, 8.48; found: C, 76.23, H, 4.68, N, 8.47.

2.4.9 5-(3'-Fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2.11)

The same method as **2.9** was used but bis(3-fluorophenyl)iodonium tetrafluoroborate (0.36 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.045 g, 0.19 mmol) and the final product was obtained (0.095 g, 72 %) as a white powder.

^1H -NMR (500 MHz) DMSO- d_6 : δ = 10.36 (s, 1H), 7.59 (dd, J = 1.8 Hz, $^3J_{\text{FH}}$ = 7.2, 1H), 7.56 (dd, J = 7.4, 1.7 Hz, 1H), 7.54 (dd, J = 7.4, 1.5 Hz, 1H), 7.36 (dd, J = 7.5, 1.5 Hz, 1H), 7.21 (ddd, J = 8.5, 1.6 Hz, $^3J_{\text{FH}}$ = 7.1, 1H), 7.15 – 7.10 (m, 1H), 6.92 – 6.87 (m, 1H), 6.86 – 6.80 (m, 2H), 6.73 (dd, J = 7.7, 1.6 Hz, 2H), 6.70 (d, J = 10.0 Hz, 1H), 4.05 (s, 2H).

^{13}C -NMR (126 MHz) DMSO- d_6 : δ = 172.0, 169.8, 161.8 (d, $^1J_{\text{FC}}$ = 243.9 Hz), 142.9 (d, $^3J_{\text{FC}}$ = 8.0 Hz), 140.2, 139.8, 139.3, 131.5, 130.9, 130.2, 130.1, 129.9 (d, $^3J_{\text{FC}}$ = 8.4 Hz), 129.5, 128.2, 128.1, 124.9, 122.7, 120.6, 115.3 (d, $^2J_{\text{FC}}$ = 21.9 Hz), 113.9 (d, $^2J_{\text{FC}}$ = 21.0 Hz), 57.3. ^{19}F -NMR (376 MHz) DMSO- d_6 : δ = -113.4 (1F).

HRMS-ESI (m/z) Calculated for $C_{21}H_{15}FN_2O$ $[+H]^+$: 331.1241, found: 331.1239. LCMS purity (UV) = 100 %, tR 12.19 min.

2.4.10 5-(3'-Trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.12**)

The same method as **2.9** was used but bis(3-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, was recovered (0.022 g, 0.09 mmol) and the final product was obtained (0.119 g, 63 %) as a white powder.

1H -NMR (500 MHz) DMSO- d_6 : δ = 10.22 (s, 1H), 7.63 – 7.53 (m, 3H), 7.42 (d, J = 7.9 Hz, 1H), 7.38 (dd, J = 7.4, 1.5 Hz, 1H), 7.34 (pt, J = 7.9 Hz, 1H), 7.20 – 7.14 (m, 3H), 6.85 – 6.79 (m, 2H), 6.75 (dd, J = 8.2, 1.5 Hz, 1H), 4.03 (s, 2H).

^{13}C -NMR (126 MHz) DMSO- d_6 : δ = 171.7, 169.8, 141.6, 140.1, 139.9, 139.2, 132.6, 131.5, 130.9, 130.2 (2C), 129.6, 129.1, 129.0 (q, $^2J_{FC}$ = 31.8 Hz), 128.4, 128.0, 125.0 (q, $^3J_{FC}$ = 3.7 Hz), 124.3 (q, $^1J_{FC}$ = 272.6 Hz), 123.8 (q, $^3J_{FC}$ = 3.7 Hz), 122.6, 120.6, 57.4.

^{19}F -NMR (376 MHz) DMSO- d_6 : δ = -61.2 (s, 3F).

HRMS-ESI (m/z) Calculated for $C_{22}H_{15}F_3N_2O$ $[+H]^+$: 381.1209, found: 381.1211. Elemental Analysis: Calculated for $C_{22}H_{15}F_3N_2O \cdot 0.3 CH_2Cl_2$ (%): C, 66.00, H, 3.87, N, 6.90; found: C, 66.19, H, 3.97, N, 6.99.

2.4.11 5-(4'-Trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.13**)

The same method as **2.9** was used but bis(4-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, was recovered (0.036 g, 0.15 mmol) and the final product was obtained (0.097 g, 58%) as a white powder.

^1H -NMR (500 MHz) DMSO- d_6 : δ = 10.46 (s, 1H), 7.62 (pt, J = 6.7 Hz, 2H), 7.59 – 7.53 (m, 1H), 7.44 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.18 (pt, J = 7.6 Hz, 1H), 7.13 (d, J = 7.8 Hz, 2H), 6.80 (d, J = 7.8 Hz, 2H), 6.75 (d, J = 7.9 Hz, 1H), 4.05 (s, 2H).

^{13}C -NMR (126 MHz) DMSO- d_6 : δ = 171.7, 169.9, 144.6, 140.1, 139.7, 139.3, 131.5, 131.2, 130.4, 130.3, 129.5, 129.4 (2C), 128.5, 128.1, 127.7 (q, $^2J_{\text{FC}}$ = 31.6 Hz), 124.9 (q, $^3J_{\text{FC}}$ = 4.1 Hz, 2C), 124.6 (q, $^1J_{\text{FC}}$ = 272.8 Hz), 122.8, 120.6, 57.3. ^{19}F -NMR (376 MHz) DMSO- d_6 : δ = -61.0 (s, 3F).

HRMS-ESI (m/z) Calculated for $\text{C}_{22}\text{H}_{15}\text{F}_3\text{N}_2\text{O}$ [$+\text{H}$] $^+$: 381.1209, found: 381.1206. Elemental Analysis: Calculated for $\text{C}_{22}\text{H}_{15}\text{F}_3\text{N}_2\text{O}$ (%): C, 69.47, H, 3.98, N, 7.36; found: C, 69.30, H, 3.88, N, 7.44.

2.4.12 5-(4'-Methoxybiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.14**)

The same method as **2.9** was used but 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (0.095 g, 0.40 mmol) and bis(4-methoxyphenyl)iodonium tetrafluoroborate (0.26 g, 0.60 mmol) were used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was recovered (0.016 g, 0.07 mmol) and the final product was obtained (0.039 g, 35%) as a white powder.

^1H -NMR (500 MHz) CDCl_3 : δ = 8.36 (s, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.28 (d, J = 7.5 Hz, 1H), 7.16 (pt, J = 7.7 Hz, 1H), 6.94 – 6.80 (m, 4H), 6.70 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 8.1 Hz, 2H), 4.30 (s, 2H), 3.72 (s, 3H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 173.2, 170.5, 158.6, 141.6, 137.3, 133.3, 131.2, 130.0, 130.1, 129.9, 129.8 (2C), 129.7, 129.6, 127.0, 123.2, 120.0, 113.1 (2C), 110.0, 56.3, 55.3.

HRMS-ESI (m/z) Calculated for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$ [$+\text{H}$] $^+$: 343.1441, found: 343.1447. LCMS purity (UV) = 99 %, tR 10.49 min.

2.4.13 5-(3'-Methylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2.15**)

The same method as **2.9** was used but 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.100 g, 0.42 mmol) and (3-methylphenyl)(2,4,6-trimethylphenyl)iodonium triflate (0.31 g, 0.62 mmol) were used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.012 g, 0.05 mmol) and the final product was obtained (0.070 g, 58%) as a white powder.

¹H-NMR (500 MHz) CDCl₃: δ = 8.41 (s, 1H), 7.71 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.31 – 7.28 (m, 1H), 7.17 – 7.12 (m, 1H), 6.96 – 6.91 (m, 1H), 6.88 – 6.81 (m, 3H), 6.78 – 6.73 (m, 2H), 6.67 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.29 (s, 2H), 2.18 (s, 3H).

¹³C-NMR (126 MHz) CDCl₃: δ = 173.2, 170.7, 142.2, 140.6, 139.6, 137.4, 137.1, 131.0, 129.9, 129.8, 129.7, 129.6, 129.5, 128.8, 127.4, 127.3, 127.2, 125.8, 123.0, 119.9, 56.4, 21.1.

HRMS-ESI (*m/z*) Calculated for C₂₂H₁₈N₂O [*+H*]⁺: 327.1492, found: 327.1483. Elemental Analysis: Calculated for C₂₂H₁₈N₂O (%): C, 80.96, H, 5.56, N, 8.5; found: C, 80.93, H, 5.42, N, 8.65.

2.4.14 3-Benzyl-5-(2'-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2.16**)

The same method as **2.9** was used but 3-benzyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.17 g, 0.52 mmol) instead of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, and bis(2-fluorophenyl)iodonium tetrafluoroborate (0.29 g, 0.78 mmol) was used instead of diphenyliodonium tetrafluoroborate and the reaction was carried out at 150 °C. The final product was obtained (0.090 g, 41%) as a white powder.

¹H-NMR (500 MHz) CDCl₃: δ = 7.83 (s, 1H), 7.57 – 7.43 (m, 3H), 7.37 – 7.24 (m, 5H), 7.24 – 6.87 (m, 7H), 6.73 (pt, *J* = 9.1 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.75 – 3.54 (m, 2H), 3.35-3.40 (m, 1H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 170.3, 170.1, 158.8 (d, $^1J_{\text{FC}}$ = 247.1 Hz), 139.9, 139.2, 136.8, 135.8, 131.7, 131.2, 130.8, 130.5, 129.9, 129.8 (2C), 129.5, 128.9 (d, $^3J_{\text{FC}}$ = 8.2 Hz), 128.5 (d, $^3J_{\text{FC}}$ = 4.0 Hz), 128.4, 128.3, 128.2 (2C), 128.1, 126.1, 123.3, 120.0, 114.9 (d, $^2J_{\text{FC}}$ = 21.8 Hz), 64.8, 37.4. ^{19}F -NMR (376 MHz) DMSO-d_6 : δ = -115.9 (s, 1F).

HRMS-ESI (m/z) Calculated for $\text{C}_{28}\text{H}_{21}\text{FN}_2\text{O}$ $[\text{+H}]^+$: 421.1711, found: 421.1709.
Elemental Analysis: Calculated for $\text{C}_{28}\text{H}_{21}\text{FN}_2\text{O}$ (%): C, 79.98, H, 5.13, N, 6.66; found: C, 79.85, H, 4.97, N, 6.73.

2.4.15 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (Nordazepam)

5-Chloro-2-aminobenzophenone (0.621 g, 3.15 mmol), N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (0.604 g, 3.15 mmol) and N-Boc-glycine (0.550 g, 3.15 mmol) were combined in toluene (6 mL) and irradiated in the microwave for 30 min at 150 °C. Trifluoroacetic acid (2 mL) was then added to the mixture and it was irradiated for a further 20 min at 150 °C. The cooled solution was neutralized by an aqueous 3 N NaOH solution (50 mL) and extracted with dichloromethane (3 x 30 mL). The organic layers were dried over MgSO_4 and evaporated. The crude material was purified by column chromatography (ethyl acetate: DCM, 10% to 40%) and the final product was obtained (0.29 g, 34 %) as a white solid powder.

^1H -NMR (500 MHz) CDCl_3 : δ = 9.41 (s, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.50 – 7.44 (m, 2H), 7.41 (pt, J = 7.5 Hz, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 4.33 (s, 2H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 171.7, 169.8, 138.7, 137.3, 131.8, 130.7, 130.6, 129.6 (2C), 128.9, 128.5, 128.4 (2C), 122.6, 56.5.

HRMS-ESI (m/z) Calculated for $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}$ $[\text{+H}]^+$: 271.0633, found: 271.0627.
LCMS purity (UV) = 100 %, tR 12.40 min.

2.4.16 7-Chloro-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2.17)

The same method as **2.9** was used but 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.16 g, 0.6 mmol) was used instead of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.010 g, 0.04 mmol) and the final product was obtained (0.118 g, 61%) as a white powder.

¹H-NMR (500 MHz) DMSO-*d*₆: δ = 10.44 (s, 1H), 7.63 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.54 – 7.50 (m, 1H), 7.36 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.21 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.12 (dd, *J* = 8.1, 6.5 Hz, 2H), 7.10 – 7.05 (m, 1H), 6.91 (dd, *J* = 7.2, 1.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 4.09 (s, 2H).

¹³C-NMR (126 MHz) DMSO-*d*₆: δ = 170.8, 169.4, 141.6, 140.5, 139.0, 138.2, 131.2, 131.1, 130.5, 130.3, 129.6, 128.5 (2C), 128.4, 128.2 (2C), 127.8, 127.2, 126.4, 122.7, 57.4.

HRMS-ESI (*m/z*) Calculated for C₂₁H₁₅ClN₂O [*+H*]⁺: 347.0946, found: 347.0947. Elemental Analysis: Calculated for C₂₁H₁₅ClN₂O (%): C, 72.73, H, 4.36, N, 8.08; found: C, 72.63, H, 4.26, N, 8.15.

2.4.17 7-Chloro-5-(4'-nitrobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2.18)

The same method as for **2.17** was used but (4-nitrophenyl)-(2,4,6-trimethylphenyl) iodonium triflate (0.47 g, 0.9 mmol) was used instead of of diphenyliodonium tetrafluoroborate. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one recovered (0.040 g, 0.15 mmol) and the final product was obtained (0.099 g, 55 %) as a white powder.

¹H-NMR (500 MHz) DMSO-*d*₆: δ = 10.51 (s, 1H), 8.08 – 7.91 (m, 3H), 7.70 – 7.65 (m, 1H), 7.64 – 7.61 (m, 1H), 7.44 – 7.40 (m, 1H), 7.27 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 4.09 (s, 2H).

^{13}C -NMR (126 MHz) DMSO- d_6 : δ = 170.1, 169.4, 144.6, 140.1, 139.6, 139.1, 138.1, 131.5, 131.1, 130.7, 130.1, 129.9, 129.7, 129.1, 128.6, 126.7, 125.4, 124.9, 123.8, 122.6, 57.4.

HRMS-ESI (m/z) Calculated for $\text{C}_{21}\text{H}_{14}\text{N}_3\text{O}_3$ [$+\text{H}$] $^+$: 392.0013, found: 392.0008. LCMS purity (UV) = 94 %, tR 17.03 min.

2.4.18 7-Chloro-5-(2'-fluorobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.19**)

The same method as **2.17** was used but bis(2-fluorophenyl)lodonium tetrafluoroborate (0.36 g, 0.9 mmol) was used instead of diphenyllodonium tetrafluoroborate. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, was recovered (0.010 g, 0.04 mmol) to give the final product (0.13 g, 64%) as a white powder and the diarylated product **5c'** was collected as a white powder (0.026 g, 10%).

^1H -NMR (500 MHz) DMSO- d_6 : δ = 10.37 (s, 1H), 7.66 – 7.61 (m, 1H), 7.59 – 7.54 (m, 2H), 7.34 (d, J = 7.3 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.21 – 7.11 (m, 1H), 6.97 (pt, J = 7.5 Hz, 1H), 6.91 (d, J = 9.5 Hz, 1H), 6.87 (dd, J = 6.8 Hz, $^3J_{\text{FH}}$ = 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 4.03 (s, 2H).

^{13}C -NMR (126 MHz) DMSO- d_6 : δ = 169.8, 169.5, 158.7 (d, $^1J_{\text{FC}}$ = 244.8 Hz), 139.82, 138.1, 135.5, 131.4, 131.2, 131.1, 130.9, 130.2, 129.8 (d, $^3J_{\text{FC}}$ = 8.0 Hz), 129.6, 129.2, 128.6 (d, $^3J_{\text{FC}}$ = 9.8 Hz), 128.0 (d, $^2J_{\text{FC}}$ = 15.6 Hz), 126.6, 124.3 (d, $^4J_{\text{FC}}$ = 3.5 Hz), 122.7, 115.3 (d, $^2J_{\text{FC}}$ = 22.1 Hz), 57.3. ^{19}F -NMR (376 MHz) DMSO- d_6 : δ = -120.4 (1F).

HRMS-ESI (m/z) Calculated for $\text{C}_{21}\text{H}_{14}\text{FN}_2\text{O}$ [$+\text{H}$] $^+$: 365.0851, found: 365.0847. Elemental Analysis: Calculated for $\text{C}_{21}\text{H}_{14}\text{FN}_2\text{O}$ (%): C, 69.14, H, 3.87, N, 7.68; found: C, 68.93, H, 3.70, N, 7.64.

2.4.19 7-Chloro-5-(2,2'-difluorobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.20**)

^1H -NMR (500 MHz) CDCl_3 : δ = 7.77 (s, 1H), 7.59 (pt, J = 7.7 Hz, 1H), 7.44 (d, J = 7.7 Hz, 2H), 7.26 – 7.00 (m, 8H), 6.87 (pt, J = 9.2 Hz, 2H), 6.49 (d, J = 8.6 Hz, 1H), 3.85 (s, 2H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 168.3, 167.7, 159.0 (d, $^1J_{\text{FC}}$ = 243.8 Hz, 2C), 139.0, 137.9, 136.4, 131.9, 131.8, 131.1 (2C), 131.0 (2C), 129.9 (d, $^3J_{\text{FC}}$ = 8.1 Hz, 2C), 129.5, 129.3, 128.5, 128.3, 128.2, 126.5, 124.3 (d, $^4J_{\text{FC}}$ = 3.5 Hz, 2C), 122.6, 115.4 (d, $^2J_{\text{FC}}$ = 22.1 Hz, 2C), 56.9. ^{19}F -NMR (376 MHz) DMSO-d_6 : δ = -113.7 (2F).

HRMS-ESI (m/z) Calculated for $\text{C}_{27}\text{H}_{17}\text{ClF}_2\text{N}_2\text{O}$ [$+\text{H}$] $^+$: 459.1070, found: 415.1072. LCMS purity (UV) = 97 %, tR 20.38 min.

2.4.20 7-Chloro-5-(4'-trifluorobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.21**)

The same method as **2.17** was used but diphenyliodonium tetrafluoroborate (0.45 g, 0.9 mmol) was used instead of diphenyliodonium tetrafluoroborate and the reaction temperature was 145 °C. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, was recovered (0.020 g, 0.066 mmol) and the final product 5d was obtained as a white powder (0.053 g, 24%). The diarylated product 5d' (0.045 g, 15%) was collected as a brown powder.

^1H -NMR (500 MHz) CDCl_3 : δ = 8.27 (s, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.59 (dd, J = 6.7, 6.0 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.0 Hz, 1H), 7.11 (d, J = 7.9 Hz, 3H), 6.82 (s, 1H), 6.59 (d, J = 8.6 Hz, 1H), 4.30 (s, 2H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 171.1, 170.1, 144.5, 140.6, 138.9, 136.0, 131.4, 130.4, 130.3, 129.8, 129.2, 129.0 (q, $^2J_{\text{FC}}$ = 33.0 Hz), 129.0 (2C), 128.7, 128.4, 124.5 (q, $^3J_{\text{FC}}$ = 3.7 Hz, 2C), 124.0 (q, $^1J_{\text{FC}}$ = 272.4 Hz), 121.3, 121.2, 56.4. ^{19}F -NMR (376 MHz) DMSO-d_6 : δ = -63.2 (s, 3F).

HRMS-ESI (m/z) Calculated for $\text{C}_{22}\text{H}_{14}\text{ClF}_3\text{N}_2\text{O}$ [$+\text{H}$] $^+$: 415.0820, found: 415.0819. LCMS purity (UV) = 95 %, tR 19.59 min.

2.4.21 7-Chloro-5-(4,4''-trifluorobiphenyl-2,6-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2.22**)

¹H-NMR (500 MHz) DMSO-d₆: δ = 10.43 (s, 1H), 7.69 (pt, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 4H), 7.50 (d, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 4H), 7.26 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 3.71 (s, 2H).

¹³C-NMR (126 MHz) DMSO-d₆: δ = 168.4, 168.3, 145.0, 141.1, 138.3, 137.4, 131.6, 130.6 (2C), 130.2, 129.9 (4C), 129.6, 128.4, 127.9 (q, ²*J*_{FC} = 33.0 Hz, 2C), 126.7, 125.1 (q, ³*J*_{FC} = 3.7 Hz, 4C), 124.6 (q, ¹*J*_{FC} = 270.4 Hz, 2C), 122.5, 120.0, 118.8, 56.9. ¹⁹F-NMR (376 MHz) DMSO-d₆: δ = -65.2 (s, 6F).

HRMS-ESI (m/z) Calculated for C₂₉H₁₇ClF₆N₂O [*+H*]⁺: 559.1006, found: 559.1003. LCMS purity (UV) = 96 %, tR 24.92 min.

2.4.22 1-Methyl-5-biphenyl-2-yl-1,3-dihydro-2*D*-1,4-benzodiazepin-2-one (**2.7**)

Compound **2.1** was stirred in acetic acid-d₄ at 125 °C in the microwave for 1 hour. Thereafter, the reaction was cooled, and the white product was collected in quantitative yield by evaporating the solvent.

¹H-NMR (500 MHz) CDCl₃: δ = 7.81 – 7.72 (m, 1H), 7.56 – 7.45 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.22 (pt, *J* = 7.9 Hz, 1H), 7.09 – 6.98 (m, 3H), 6.92 – 6.82 (m, 5H), 3.13 (s, 3H).

¹³C-NMR (126 MHz) CDCl₃: δ = 173.2, 169.4, 142.9, 142.2, 138.4, 131.2, 130.5, 130.2, 130.0, 129.9, 129.2, 128.7 (2C), 127.7 (2C), 127.5, 126.5, 123.4, 120.1, 55.5 (m), 34.9.

²H-NMR (61 MHz) CH₃CO₂H: δ = 4.95 (1H), 3.94 (1H).

HRMS-ESI (m/z) Calculated for C₂₁H₁₆D₂N₂O [*+H*]⁺: 329.1617, found: 329.1614.

2.4.23 5-(2'-Fluorobiphenyl-2-yl)-1,3-dihydro-2*D*-1,4-benzodiazepin-2-one (2.23)

The same method as for the synthesis of **2.19** was used but acetic acid- d_4 (4 mL) was used instead of acetic acid as the solvent. Final product was obtained (0.09 g, 47 %) as a white powder.

$^1\text{H-NMR}$ (500 MHz) CDCl_3 : δ = 8.93 (s, 1H), 7.76 – 7.69 (m, 1H), 7.55 – 7.47 (m, 2H), 7.36 – 7.29 (m, 1H), 7.18 (pt, J = 7.7 Hz, 1H), 7.05 – 6.83 (m, 5H), 6.72 (m, 2H).

$^{13}\text{C-NMR}$ (126 MHz) CDCl_3 : δ = 172.3, 171.0, 158.8 ($^1J_{\text{CF}} = 246.8$ Hz), 140.2, 137.3, 135.7, 131.4 (d, $^3J_{\text{FC}} = 3.9$ Hz), 131.2, 130.8, 130.0, 129.8, 129.5, 129.1 (d, $^3J_{\text{FC}} = 7.9$ Hz), 128.6, 128.1 (d, $^2J_{\text{FC}} = 15.4$ Hz), 127.9, 123.3 (d, $^4J_{\text{FC}} = 3.6$ Hz), 123.2, 120.2, 114.9 (d, $^2J_{\text{FC}} = 22.2$ Hz), 56.0 (m). $^2\text{H-NMR}$ (61 MHz) $\text{CH}_3\text{CO}_2\text{H}$: δ = 4.27 (s, 2H).

HRMS-ESI (m/z) Calculated for $\text{C}_{21}\text{H}_{13}\text{D}_2\text{FN}_2\text{O}$ [$+\text{H}$] $^+$: 333.1210, found: 333.1362. LCMS purity (UV) = 97 %, tR 11.06 min.

2.4.24 5-Biphenyl-2-yl-1,3-dihydro-2*D*-1,4-benzodiazepin-2-one (2.24)

The same method as **2.7** was used and the product was collected in quantitative yield.

$^1\text{H-NMR}$ (500 MHz) $\text{DMSO-}d_6$: δ = 10.31 (s, 1H), 7.58 – 7.52 (m, 2H), 7.48 (d, J = 7.4 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.15 (pt, J = 7.4 Hz, 1H), 7.10 – 7.03 (m, 3H), 6.91 (d, J = 7.1 Hz, 2H), 6.81 – 6.75 (m, 2H), 6.70 (d, J = 7.9 Hz, 1H).

$^{13}\text{C-NMR}$ (126 MHz) $\text{DMSO-}d_6$: δ = 173.2, 169.6, 141.5, 140.5, 139.8, 139.2, 131.3, 130.9, 130.2, 130.1, 129.4, 128.6 (2C), 128.3, 128.0 (2C), 127.6, 127.1, 122.6, 120.7, 57.0. $^2\text{H-NMR}$ (61 MHz) $\text{CH}_3\text{CO}_2\text{H}$: δ = 4.44 (2H).

HRMS-ESI (m/z) Calculated for $\text{C}_{21}\text{H}_{14}\text{D}_2\text{N}_2\text{O}$ [$+\text{H}$] $^+$: 315.1445, found: 315.1453.

2.4.25 5-(3'-Trifluorobiphenyl-2-yl)-1,3-dihydro-2*D*-1,4-benzodiazepin-2-one (2.25)

The same method as **2.17** was used and the product was collected in quantitative yield.

^1H -NMR (500 MHz) DMSO- d_6 : δ = 10.20 (s, 1H), 7.61 – 7.51 (m, 3H), 7.43 – 7.28 (m, 3H), 7.19 – 7.10 (m, 3H), 6.80 (dd, J = 8.4, 5.1 Hz, 2H), 6.72 (d, J = 7.9 Hz, 1H).

^{13}C -NMR (126 MHz) DMSO- d_6 : δ = 171.7, 169.8, 141.6, 140.1, 139.9, 139.2 (2C), 132.6, 131.5, 130.9, 130.2, 129.6, 129.1 (q, $^2J_{\text{FC}}$ = 31.7 Hz), 129.0, 128.4, 127.9, 124.9 (q, $^3J_{\text{FC}}$ = 3.7 Hz), 124.3 (q, $^1J_{\text{FC}}$ = 273.2 Hz), 123.8 (q, $^3J_{\text{FC}}$ = 3.8 Hz), 122.6, 120.5, 56.5 (CD_2).
 ^2H -NMR (61 MHz) $\text{CH}_3\text{CO}_2\text{H}$: δ = 4.40 (2H).

HRMS-ESI (m/z) Calculated for $\text{C}_{22}\text{H}_{13}\text{D}_2\text{F}_3\text{N}_2\text{O}$ [$+\text{H}$] $^+$: 315.1445, found: 315.1453

2.4.26 7-Chloro-1-methyl-5-(2'-fluorobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (2.26)

7-Chloro-5-(2'-fluorobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one 5c (0.035 g, 0.096 mmol) was dissolved in MeOH/THF (1 mL). Potassium carbonate (0.079 g, 0.57 mmol), iodomethane (0.03 mL, 0.48 mmol) were added and the reaction was stirred overnight at room temperature (rt). Thereafter the reaction mixture was filtered over celite, washed through with dichloromethane and concentrated under reduced pressure. The final product was collected as a white powder (0.033 g, 91%).

^1H -NMR (500 MHz) CDCl_3 : δ = 7.79 – 7.73 (m, 1H), 7.54 (dd, J = 6.3, 3.1 Hz, 2H), 7.34 – 7.28 (m, 1H), 7.19 (dd, J = 8.9, 2.5 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.96 – 6.88 (m, 3H), 6.83 (d, J = 8.9 Hz, 1H), 6.80 – 6.73 (m, 1H), 4.79 (d, J = 10.9 Hz, 1H), 3.66 (d, J = 10.9 Hz, 1H), 3.11 (s, 3H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 170.3, 169.3, 158.9 (d, $^1J_{\text{FC}}$ = 247.7 Hz), 141.3, 138.9, 135.6, 131.4, 131.3, 131.0 (d, $^3J_{\text{FC}}$ = 8.0 Hz), 130.8, 130.4, 129.9, 128.9, 128.8 (d, $^3J_{\text{FC}}$ = 8.0 Hz), 128.7, 128.5 (d, $^2J_{\text{FC}}$ = 15.9 Hz), 128.3, 123.4 (d, $^4J_{\text{FC}}$ = 3.6 Hz), 121.4, 115.1 (d, $^2J_{\text{FC}}$ = 22.2 Hz), 56.7, 35.0.

HRMS-ESI (m/z) Calculated for $\text{C}_{22}\text{H}_{16}\text{ClFN}_2\text{O}$ [$+\text{H}$] $^+$: 379.1008, found: 379.1012.
 LCMS purity (UV) = 98 %, tR 18.09 min.

2.4.27 7-Chloro-1-prop-2-yn-1-yl-5-biphenyl-2-yl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2.27**)

7-Chloro-5-biphenyl-2-yl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (0.025 g, 0.072 mmol) was dissolved in MeOH/THF (1 mL). Potassium carbonate (0.060 g, 0.43 mmol), propargyl bromide (0.027 mL, 0.30 mmol) were added and the reaction was stirred overnight at rt. Thereafter the reaction mixture was filtered over celite, washed through with dichloromethane and concentrated under reduced pressure. The final product was collected as a white powder (0.024 g, 88 %).

¹H-NMR (500 MHz) DMSO-d₆: δ = 7.64 (d, J = 7.6 Hz, 1H), 7.59 (pt, J = 7.6 Hz, 1H), 7.53 (pt, J = 7.6 Hz, 1H), 7.41 (dd, J = 8.9, 2.3 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.19 – 7.12 (m, 3H), 6.86 (d, J = 7.0 Hz, 2H), 6.67 (d, J = 2.5 Hz, 1H), 4.81 (d, J = 17.5 Hz, 1H), 4.58 (d, J = 10.9 Hz, 1H), 3.74 (d, J = 10.9 Hz, 1H), 3.43 (d, J = 17.5 Hz, 1H), 3.37 (s, 1H).

¹³C-NMR (126 MHz) DMSO-d₆: δ = 170.8, 168.1, 141.7, 140.9, 140.7, 138.2, 131.6, 131.3, 130.1, 130.7, 130.4, 128.6 (2C), 128.4 (2C), 128.3, 128.1, 128.0, 127.3, 121.8, 80.2, 75.2, 56.7, 38.0.

HRMS-ESI (m/z) Calculated for C₂₄H₁₇ClN₂O [$+H$]⁺: 385.1102, found: 385.1108.
LCMS purity (UV) = 96 %, tR 20.90 min.

2.5 Reference

- 1 D. H. Wang and J. Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 5767–5769.
- 2 X. Huang, T. M. Bergsten and J. T. Groves, *J. Am. Chem. Soc.*, 2015, **137**, 5300–5303.
- 3 J. He, L. G. Hamann, H. M. L. Davies and R. E. J. Beckwith, *Nat. Commun.*, 2015, **6**, 5943-5952, DOI:10.1038/ncomms6943.
- 4 J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369–375.
- 5 A. Sharma and J. F. Hartwig, *Nature*, 2015, **517**, 600–604.
- 6 A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature.*, 2014, **510**, 129–133.

- 7 A. C. Kruegel, S. Rakshit, X. Li and D. Sames, *J. Org. Chem.*, 2015, **80**, 2062–2071.
- 8 X. Lu, B. Xiao, R. Shang and L. Liu, *Chinese Chem. Lett.*, 2016, **27**, 305–311.
- 9 F. O'Hara, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2013, **135**, 12122–12134.
- 10 B. Liégault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047–1060.
- 11 D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian and K. Fagnou, *J. Org. Chem.*, 2011, **76**, 749–759.
- 12 S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886–896.
- 13 J. M. Schulman, A. A. Friedman, J. Panteleev and M. Lautens, *Chem. Commun.*, 2012, **48**, 55–57.
- 14 J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem.*, 2012, **124**, 9092–9142.
- 15 J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem. Int. Ed.*, 2012, **51**, 8960–9009.
- 16 R. B. Bedford, J. G. Bowen and A. L. Weeks, *Tetrahedron*, 2013, **69**, 4389–4394.
- 17 J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109–4112.
- 18 S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936–946.
- 19 J. Spencer, R. P. Rathnam and B. Z. Chowdhry, *Future Med. Chem.*, 2010, **2**, 1441–1449.
- 20 J. Spencer, R. P. Rathnam, A. L. Harvey, C. J. Clements, R. L. Clark, M. P. Barrett, P. E. Wong, L. Male, S. J. Coles and S. P. MacKay, *Bioorg. Med. Chem.*, 2011, **19**, 1802–1815.
- 21 R. L. Clark, C. J. Clements, M. P. Barrett, S. P. MacKay, R. P. Rathnam, G. Owusu-Dapaah, J. Spencer and J. K. Huggan, *Bioorg. Med. Chem.*, 2012, **20**, 6019–6033.
- 22 A. El Bouakher, G. Prié, M. Aadil, M. Akssira and M. C. Viaud-Massuard, *Tetrahedron*, 2013, **69**, 5086–5091.
- 23 N. Kaur and D. Kishore, *Synth. Commun.*, 2014, **44**, 1375–1413.
- 24 G. F. Field, W. J. Zally and L. H. Sternbach, *J. Am. Chem. Soc.*, 1967, **3957**, 332–338.
- 25 B. A. Bunin, M. J. Plunkett and J. A. Ellman, *Proc. Natl. Acad. Sci. U. S. A.*, 1994, **91**, 4708–4712.

- 26 P. Filippakopoulos, J. Qi, S. Picaud, Y. Shen, W. B. Smith, O. Fedorov, E. M. Morse, T. Keates, T. T. Hickman, I. Felletar, M. Philpott, S. Munro, M. R. McKeown, Y. Wang, A. L. Christie, N. West, M. J. Cameron, B. Schwartz, T. D. Heightman, N. La Thangue, C. a French, O. Wiest, A. L. Kung, S. Knapp and J. E. Bradner, *Nature*, 2010, **468**, 1067–1073.
- 27 A. Nadin, M. Sa, A. P. Owens, D. M. Howells, A. C. Talbot and T. Harrison, *J. Org. Chem.*, 2003, **2**, 2844–2852.
- 28 J. J. Liu, B. Higgins, G. Ju, K. Kolinsky, K. C. Luk, K. Packman, G. Pizzolato, Y. Ren, K. Thakkar, C. Tovar, Z. Zhang and P. M. Wovkulich, *ACS Med. Chem. Lett.*, 2013, **4**, 259–263.
- 29 O. Mirguet, R. Gosmini, J. Toum, C. A. Clément, M. Barnathan, J. M. Brusq, J. E. Mordaunt, R. M. Grimes, M. Crowe, O. Pineau, M. Ajakane, A. Daugan, P. Jeffrey, L. Cutler, A. C. Haynes, N. N. Smithers, C. W. Chung, P. Bamborough, I. J. Uings, A. Lewis, J. Witherington, N. Parr, R. K. Prinjha and E. Nicodème, *J. Med. Chem.*, 2013, **56**, 7501–7515.
- 30 M. G. J. Baud, E. Lin-shiao, T. Cardote, C. Tallant, A. Pschibul, K. Chan, M. Zengerle, J. R. Garcia, K. Terence, F. M. Ferguson and A. Ciulli, *Science.*, 2014, **346**, 638–641.
- 31 B. Trost, *Science.*, 1991, **254**, 1471–1477.
- 32 J. Spencer, D. P. Sharratt, J. Dupont, A. L. Monteiro, V. I. Reis, M. P. Stracke, F. Rominger and I. M. McDonald, *Organometallics*, 2005, **24**, 5665–5672.
- 33 J. Spencer, B. Z. Chowdhry, A. I. Mallet, R. P. Rathnam, T. Adatia, A. Bashall and F. Rominger, *Tetrahedron*, 2008, **64**, 6082–6089.
- 34 H. Abdelkafi and J. C. Cintrat, *Sci. Rep.*, 2015, **5**, 12131–12138.
- 35 J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527–2571.
- 36 M. W. Gribble, J. A. Ellman and R. G. Bergman, *Organometallics*, 2008, **27**, 2152–2155.
- 37 J. Dupont and M. Pfeffer, *Platin. Met. Rev.*, 2009, **53**, 67–68.
- 38 A. Sharma, P. Appukkuttan and E. Van der Eycken, *Chem. Commun.*, 2012, **48**, 1623–1637.
- 39 M. Baghbanzadeh, C. Pilger and C. Oliver Kappe, *J. Org. Chem.*, 2011, **76**, 8138–8142.
- 40 E. A. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48**, 9052–9070.
- 41 C. L. Ciana, R. J. Phipps, J. R. Brandt, F. M. Meyer and M. J. Gaunt, *Angew. Chem.*

- Int. Ed.*, 2011, **50**, 458–462.
- 42 S. G. Modha and M. F. Greaney, *J. Am. Chem. Soc.*, 2015, **137**, 1416–1419.
 - 43 M. Bielawski, D. Aili and B. Olofsson, *J. Org. Chem.*, 2008, **73**, 4602–4607.
 - 44 Z. Wu, S. Chen, C. Hu, Z. Li, H. Xiang and X. Zhou, *ChemCatChem*, 2013, **5**, 2839–2842.
 - 45 Z. Liang, J. Yao, K. Wang, H. Li and Y. Zhang, *Chem. Eur. J.*, 2013, **19**, 16825–16831.
 - 46 S. Islam and I. Larrosa, *Chem. Eur. J.*, 2013, **19**, 15093–15096.
 - 47 S. J. Coles and P. A. Gale, *Chem. Sci.*, 2012, **3**, 683–689.
 - 48 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem Soc Rev*, 2008, **1**, 1–200.
 - 49 G. Algarra, W. B. Cross, D. L. Davies, Q. Khamker, S. A. Macgregor, C. L. McMullin and K. Singh, *J. Org. Chem.*, 2014, **79**, 1954–1970.
 - 50 E. T. Nadres and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 7–10.
 - 51 S. Ma, G. Villa, P. S. Thuy-Boun, A. Homs and J. Q. Yu, *Angew. Chem. Int. Ed.*, 2014, **53**, 734–737.
 - 52 W. Ma and L. Ackermann, *Chem. Eur. J.*, 2013, **19**, 13925–13928.
 - 53 S. K. Yang, R. Tang and Q. Pu, *J. Label. Compd. Radiopharm.*, 1996, **38**, 753–759.
 - 54 T. G. Gant, *J. Med. Chem.*, 2014, **57**, 3595–3611.
 - 55 L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliliw, L. O. Randall and R. Banziger, *J. Med. Chem.*, 1965, **8**, 815–821.
 - 56 G. Mwande-Maguene, J. Jakhlal, J. B. Lekana-Douki, E. Mouray, T. Bousquet, S. Pellegrini, P. Grellier, F. S. T. Ndouo, J. Lebibi and L. Pelinski, *New J. Chem.*, 2011, **35**, 2412–2415.
 - 57 C. Delvare, C. S. Harris, L. Hennequin, P. Koza, C. Lambert-Van Der Brempt, J. Pelleter and O. Willerval, *ACS Comb. Sci.*, 2011, **13**, 449–452.
 - 58 I. Chuckowree, M. Ali Syed, G. Getti, A. Parbhu Patel, H. Garner, G. J. Tizzard, S. J. Coles and J. Spencer, *Tetrahedron Lett.*, 2012, **53**, 3607–3611.
 - 59 I. M. McDonald, C. Austin, I. M. Buck, D. J. Dunstone, E. Griffin, E. a Harper, R. a D. Hull, S. B. Kalindjian, I. D. Linney, C. M. R. Low, M. J. Pether, J. Spencer, P. T. Wright, T. Adatia and A. Bashall, *J. Med. Chem.*, 2006, **49**, 2253–2261.
 - 60 I. M. McDonald, J. W. Black, I. M. Buck, D. J. Dunstone, E. P. Griffin, E. Harper, R. D. Hull, S. B. Kalindjian, E. J. Lilley, I. D. Linney, M. J. Pether, S. P. Roberts,

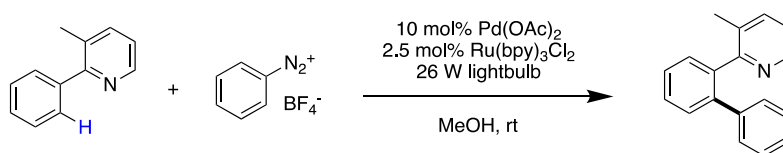
- M. E. Shaxted, J. Spencer, K. I. M. Steel, D. a Sykes, M. K. Walker, G. F. Watt, L. Wright, P. T. Wright and W. Xun, *J. Med. Chem.*, 2007, **50**, 3101–3112.
- 61 S. Yotphan, R. G. Bergman and J. a Ellman, *Org. Lett.*, 2009, **11**, 1511–1514.
- 62 P. Filippakopoulos, S. Picaud, O. Fedorov, M. Keller, M. Wrobel, O. Morgenstern, F. Bracher and S. Knapp, *Bioorg. Med. Chem.*, 2012, **20**, 1878–1886.

Chapter 3

Combining Sanford Arylations on Benzodiazepines with the Nuisance Effect

3.1 Introduction

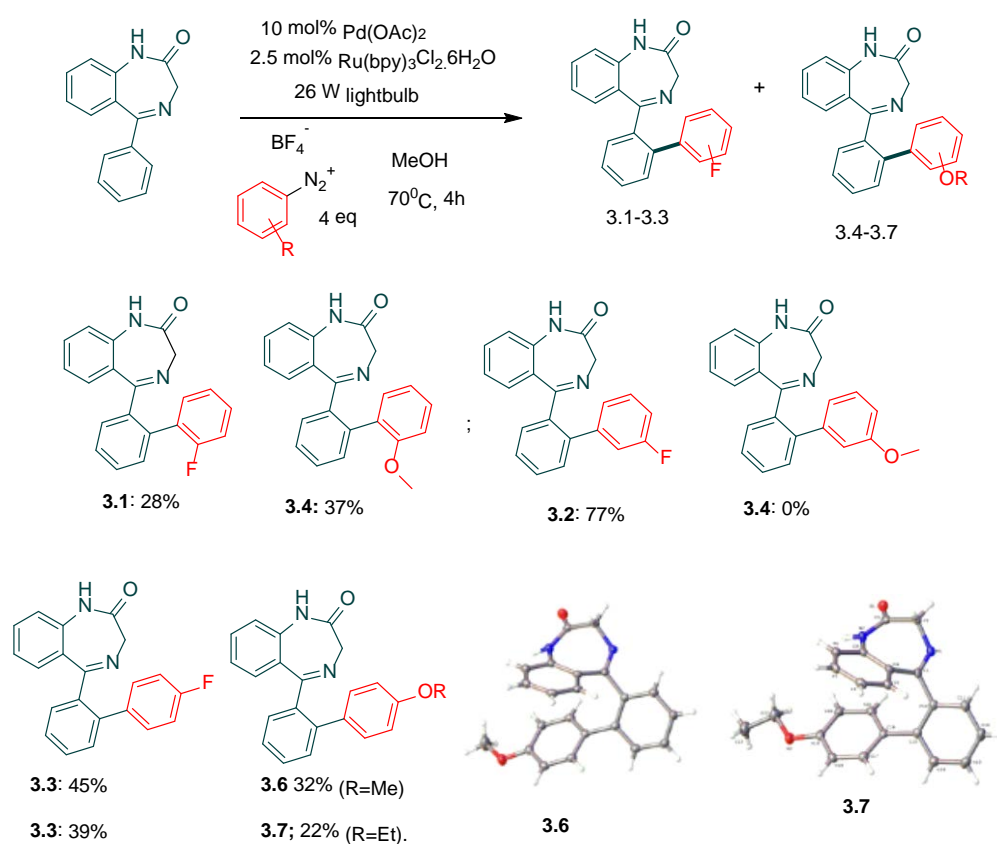
There is a growing impetus for atom economical routes to high value end products employing late stage functionalization (LSF) processes.¹ These are particularly desirable in medicinal chemistry since they increase diversity and chemical space and enable rapid SAR (structure activity relationship) and ADME-Tox (Absorption, distribution, metabolism, elimination-toxicity) feedback that is key to costly, high attrition, drug development. Late stage C-H activation is a powerful tool in generating novel compounds for biological evaluation.²⁻¹⁵ Chapter 2 described a palladium-catalyzed ortho-arylation of benzodiazepines employing iodonium salts in acetic acid under microwave irradiation.^{16,17} The harsh conditions, relatively high commercial cost, and multistep synthesis of iodonium salts¹⁸⁻²⁰ ($\text{ArI}^+\text{Ar}'^+$), coupled with a poor atom economy (Ar-I is a byproduct) prompted us to consider a visible-light photocatalyzed Pd-mediated protocol involving diazonium salts (Scheme 3.0).²¹⁻²⁵



Scheme 3.0: Visible-light photocatalyzed Pd-mediated protocol for C-H arylation

3.2 Results and Discussion

Initial reaction trials were performed on the 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one skeleton, using the 2-fluorobenzenediazonium salt under reflux. To our surprise, in addition to the expected product **3.1**, we were able to isolate the ether product **3.4**. However, reaction of the 3-fluorobenzenediazonium tetrafluoroborate led exclusively to the fluorobiaryl derivative **3.2**, whereas the 4-fluorobenzenediazonium salt afforded a mixture of fluorobiaryl **3.3** and methoxy product **3.6**. Repeating the reaction in ethanol led to the ethyl ether product **3.7**, as shown in Scheme 3.1.

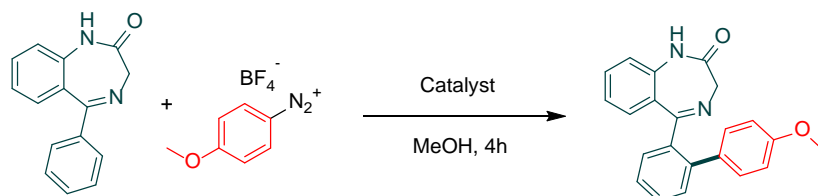


Scheme 3.1: Benzodiazepine library synthesis

Characterization of **3.6** and **3.7** were enabled by determination of its solid state x-ray structure²⁶ (Scheme 3.1) and by its unequivocal synthesis starting from 4-methoxybenzenediazonium tetrafluoroborate (Table 3.1) where we found slightly better yields under reflux (Entry 1 vs. 2) compared to either ambient temperature or to the absence of photocatalyst (Entry 5). Moreover, a palladium catalyst was essential (Entry

4) for achieving a good yield. Microwave-mediated chemistry, in the absence of light and photocatalyst, gave little conversion of product.

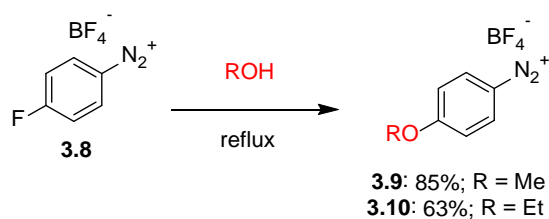
Table 3.1: Synthesis of an anisole derivative – optimisation



Entry	Lamps 26W	$Pd(OAc)_2$ (mol %)	$Ru(bpy)_3Cl_2$ 6H ₂ O(mol %)	Temp. (°C)	Conv. LC/MS (%)
1	Yes	10	2.5	rt	52
2	Yes	10	2.5	Reflux	61
3	No	10	2.5	Reflux	35
4	Yes	0	2.5	Reflux	0
5	Yes	10	0	Reflux	57
6	No	10	0	^a	20

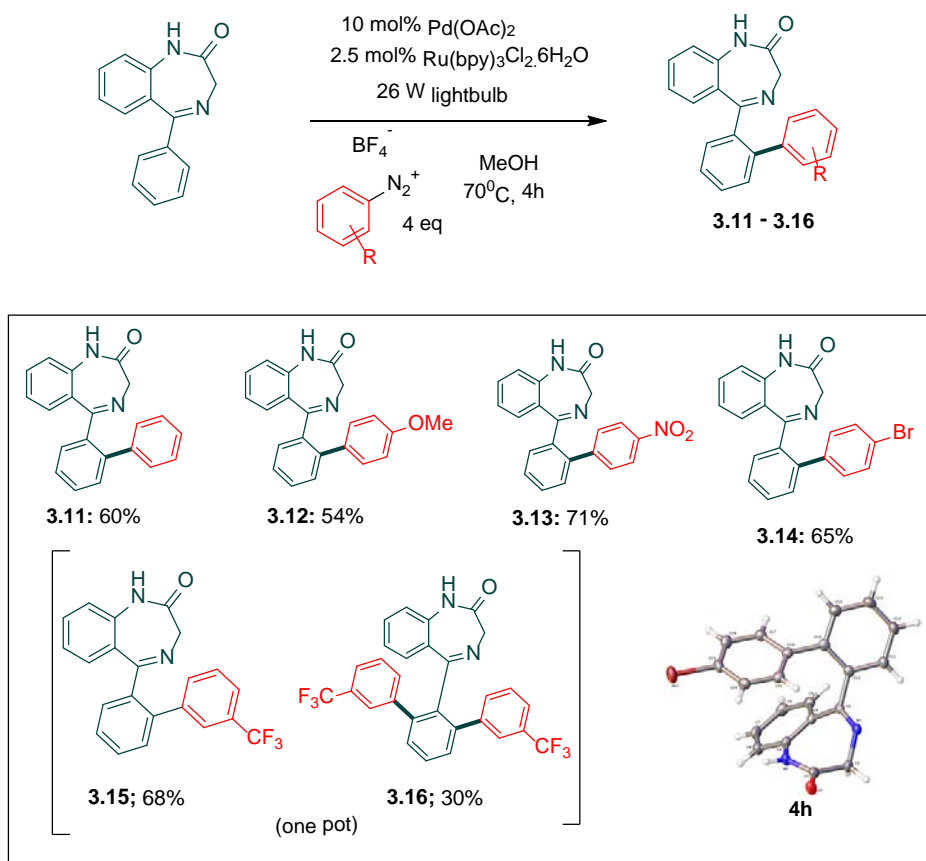
^a Microwave (MW), 125 °C, 1h.

To explain the formation of the ether products we propose a competing S_NAr (nucleophilic aromatic substitution), termed “nuisance effect,” which has historically been observed for halogen-substituted benzenediazonium salts, given the strong electron withdrawing effects of the diazo group, notably operating on the 2- and 4-substituted isomers.²⁷ Indeed, simple alcoholysis of 4-fluorobenzenediazonium tetrafluoroborate, **3.8** was achieved by reflux in the appropriate alcohol solvent (Scheme 3.2).



Scheme 3.2: “Nuisance effect” on diazonium salts.

The C-H activation reaction was also applied to aryldiazoniums incapable of undergoing such a F-substitution and, hence derivatives **3.11-3.16** were synthesized in good to excellent yields (Scheme 3.3). Indeed, yields tend to be either similar or higher than those reported for the corresponding reactions involving iodonium salts, e.g. **3.11** (60% vs. 56%), **3.12** (54% vs. 35%), **3.13** (71% vs. 55%) and **3.15** (64% vs. 63%).

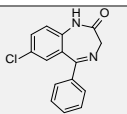
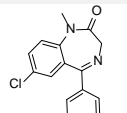
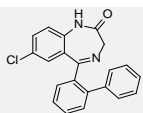
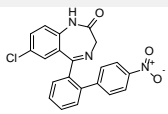
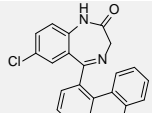
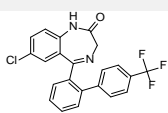


Scheme 3.3: Other arylated benzodiazepines

In the synthesis of **3.15**, relatively large amounts of the diarylated **3.16** were also observed. Such di-arylations were previously reported by us (Chapter 2).¹⁷

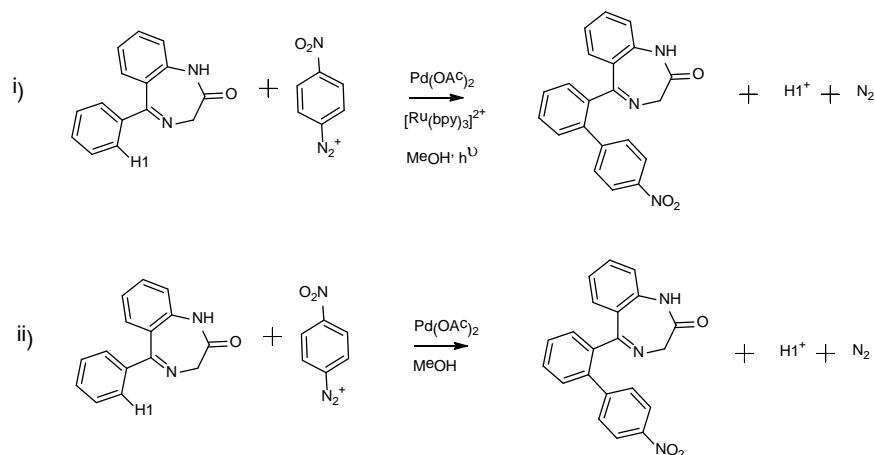
The current and previous library of benzodiazepines (Scheme 3.1) was tested for GABA binding.²⁸ None of the current benzodiazepines displayed any appreciable biological activity although 7-chloro-benzodiazepines, as expected, had reasonable activity, although were *ca.* 7-10 fold less active than nordazepam and diazepam controls (Entries 1 and 2 respectively, Table 2) and were not pursued any further.

Table 3.2: GABA_A activity of *ortho*-arylated BZDs

Entry	Compound	mean <i>K_i</i> (nM)/ SEM (nM) vs. GABA
1		51.62 ± 2.0
2		41.41 ± 4.9
3		373.45 ± 110.5
4		421.54 ± 86.1
5		303.25 ± 60.7
6		689.56 ± 480.3

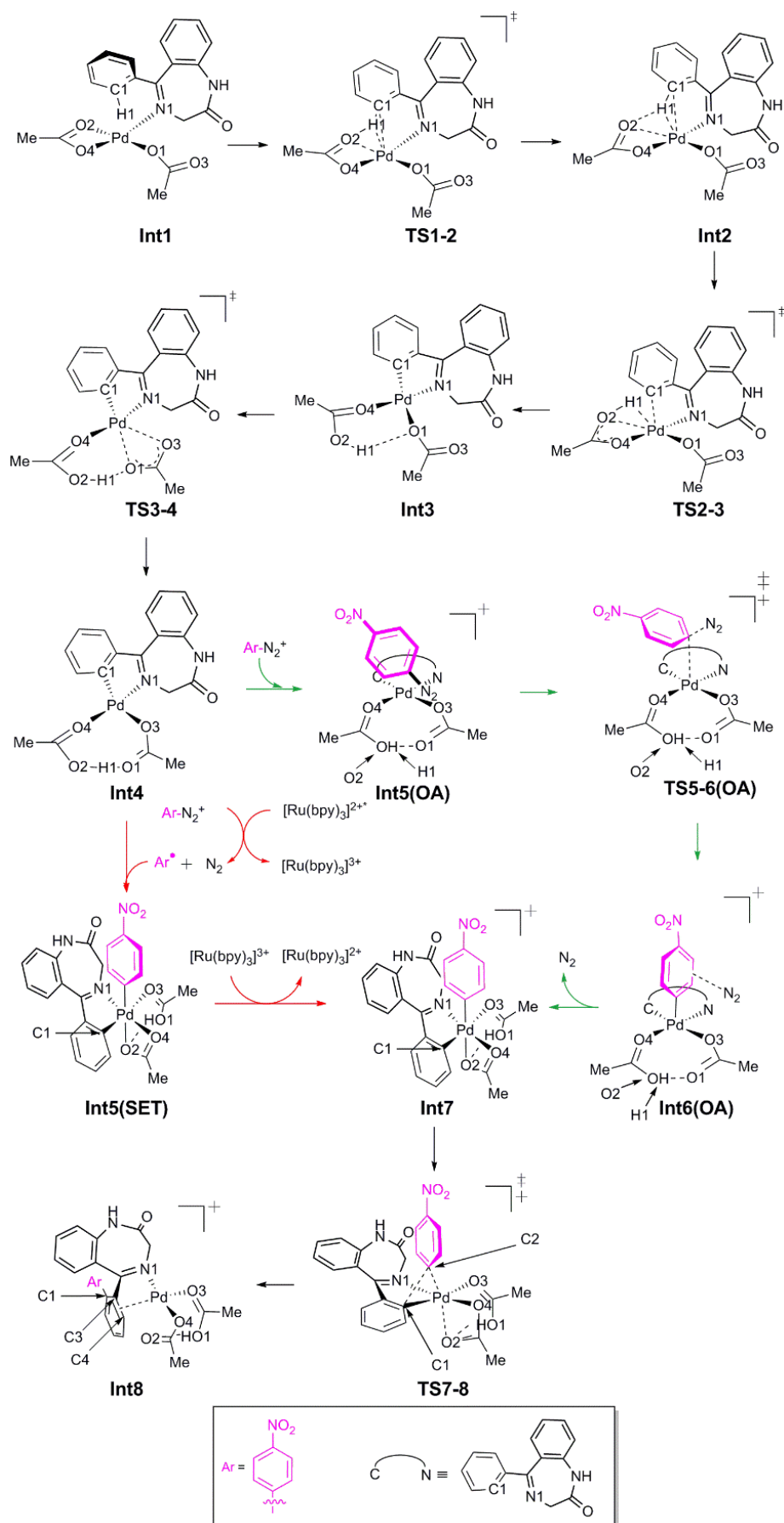
Sanford *et al.* proposed a possible mechanism to explain their Pd/Ru photocatalysed C-H arylation.²¹ Following is a computational study of a Pd-catalysed conducted by our collaborators and a Sanford-derived Pd/Ru photocatalysed mechanism for the

functionalization of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one to 5-(4'-Nitrobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, **3.13** (Scheme 3.4) to rationalise the increased yield in the presence of light and a Ru photocatalyst.



*Scheme 3.4: The formation reaction of **3.13** with (i) and without (ii) the Ru photocatalyst, investigated using DFT.*

The detailed mechanism is shown in Scheme 5 and the reaction profile (relative to the reactants) in Figure 3.1. The reaction mechanism, with and without the Ru(II)-photocatalyst, essentially follows the same path except that the oxidative addition step in the presence of just the Pd(II)-catalyst (path shown in green, Scheme 3.5 and Figure 3.1), is replaced by a single-electron-transfer (SET) process when the Ru(II)-photocatalyst is added (shown in red, Scheme 3.5 and Figure 3.1).



*Scheme 3.5: The reaction mechanism for the functionalization of benzodiazepine. From **Int4** to **Int7** the transformation follows the green path in the presence of the Pd catalyst and the red path in the presence of the Pd catalyst and the red path in the presence of the Pd/Ru catalysts*

The initial step of the catalysed mechanism involves the coordination to Pd(OAc)₂ by a N atom on the un-functionalised benzodiazepine to provide **Int1**, followed by the formation of an agostic complex **Int2** prior to C-H activation. The atomic distance between Pd and the agostic H in **Int2** is 1.903 Å, which is in good agreement with similar agostic interactions in the literature: Pd---H = 1.91 Å²⁹ and Rh---H (1.95 Å).³⁰ The barrier to C-H bond activation is 41.4 kJ mol⁻¹, and involves H migration from C to O *via* a six-membered ring (**TS2-3**). Prior to coordination with the *p*-nitrobenzenediazonium (Ar-N₂⁺) the complex undergoes an isomerisation step (**TS3-4**), which involves a change in the C1-Pd-O3 angle from 132.0 to 172.0 degrees with an energy barrier of 27.8 kJ mol⁻¹ to form **Int4**.

In the absence of the photocatalyst, Ar-N₂⁺ interacts with the Pd(II) complex and follows an oxidation addition (OA) pathway, (highlighted in green, Scheme 5 and Figure 1). The oxidative addition via **TS5-6(OA)** has an energy barrier of 127.1 kJ mol⁻¹ and involves the formation of an Ar-Pd(IV) complex. The N₂ is then eliminated leading to **Int7**.

When the Ru(II)-photocatalyst is present, the nitrobenzene radical (Ar*) is generated from Ar-N₂⁺ (via oxidative quenching of Ar-N₂⁺ by the photo-excited [Ru(bpy)₃]²⁺ complex to form [Ru(bpy)₃]³⁺³¹ and follows a single-electron-transfer (SET) pathway, (in red, Scheme 3.5 and Figure 3.1). The square planar geometry of the Pd(II) complex **Int4** becomes a Pd(III) distorted-octahedral structure when the Ar binds to the Pd centre in **Int5(SET)**; this is consistent with the crystal structure of other Pd(III)-complexes.^{32,33} **Int7** is formed directly from **Int5(SET)** by the transfer of an electron to the [Ru(bpy)₃]³⁺ complex to recover the photocatalyst. The Gibbs free energy barrier for single electron transfer (SET) resulting in the formation of the Pd(IV) complex **Int7** was calculated to be 2.5 kJ mol⁻¹ using Marcus and Savéant theor.³⁴⁻³⁸ The details of this calculation are provided in the Computational Method section. This barrier is very small but similar to literature values that range from 0.4 – 15.1 kJ mol⁻¹.³⁹

Both mechanisms (OA and SET) result in the same Pd(IV) structure for **Int7**. At this stage reductive elimination occurs via **TS7-8** with a barrier of 43.2 kJ mol⁻¹. This step involves the formation of a C-C bond to facilitate the functionalization of the benzodiazepine and the oxidation state of the Pd-center changes from Pd(IV) to Pd(II) (**Int7** → **Int8**).

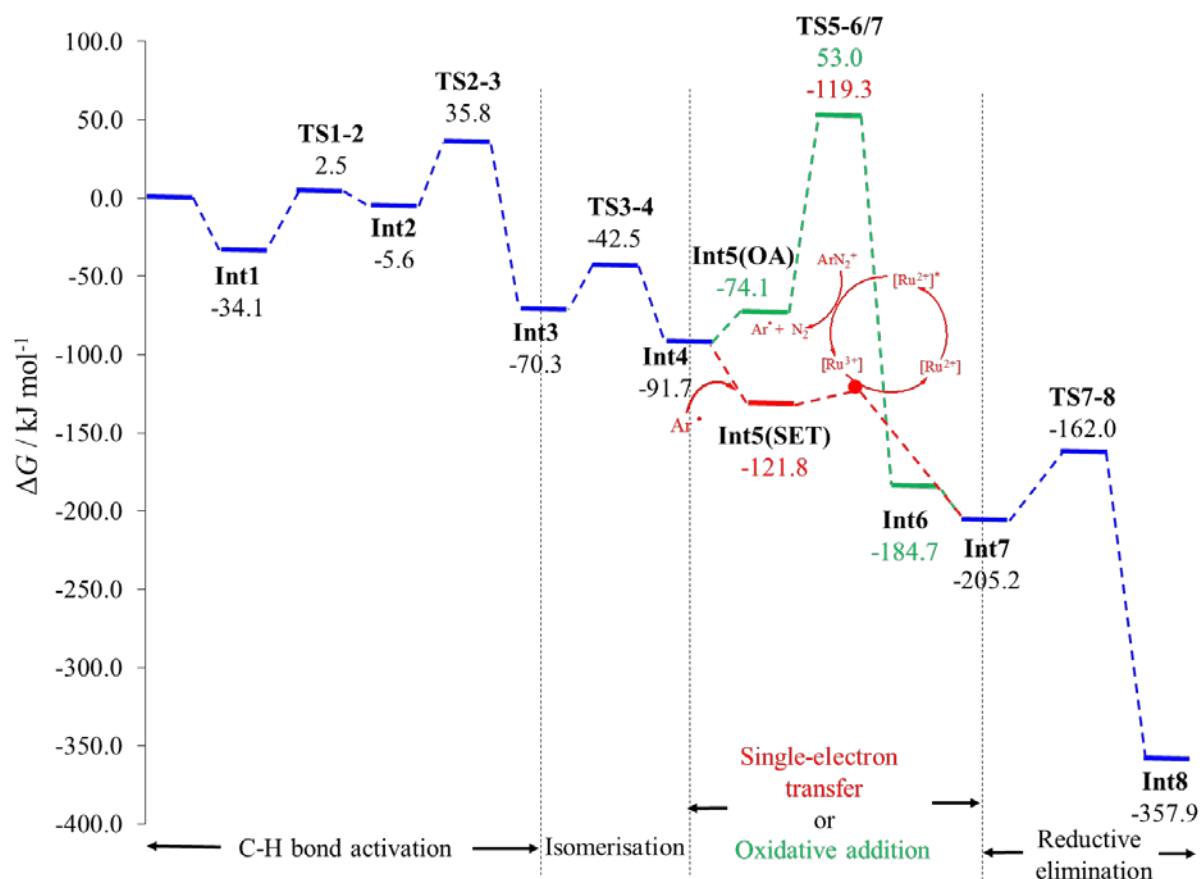


Figure 3.1: The reaction energy profile for the formation of **4g** from **1a**, with (red path) and without (green path) a photocatalyst. Steps common to both mechanisms are shown in blue. [Ru²⁺] and [Ru³⁺] represent [Ru(bpy)₃]²⁺ and [Ru(bpy)₃]³⁺, respectively

In order to facilitate the functionalization of the benzodiazepine and the oxidation state of the Pd-center changes from Pd(IV) to Pd(II) (**Int7** → **Int8**). The geometry **Int8**, involves an η^2 (C=C) interaction with Pd. A similar interaction was observed by Ariaifard *et al.*⁴⁰ and Canty *et al.*⁴¹ in their DFT calculations and in a palladium complex crystal structure.⁴²

It is clear from Figure 3.1 that in the presence of the Pd-catalyst, the oxidative addition step is rate determining with a considerable energy barrier. Large energy barrier is avoided as the reaction proceeds via a very low-energy single-electron-transfer process. This provides a rationale for the increased yield in the presence of a photocatalyst.

3.3 Conclusion

The C-H activation of benzodiazepines with 2- or 4-fluorobenzene diazonium salts under Pd catalysis with a Ru photocatalyst, in alcohol solvent, under reflux, leads to a mixture of both fluoroaryl and alkoxyaryl products. Reaction temperature is a key factor in determining the ratio of expected vs. “nuisance effect” (S_NAr) products. At ambient temperature trace amounts of the S_NAr product are detected whereas significant amounts can be obtained after prolonged heating under reflux. This process can also be extended to other aryl diazonium salts affording ortho-arylated benzodiazepines. These were tested for biological activity but were found to be significantly less active than e.g. nordazepam and diazepam controls. Density functional theory (DFT) has been used to provide a detailed mechanistic understanding of the functionalization of the benzodiazepines and to offer an explanation for the increased yield in the presence of a Ru(II)-photocatalyst. The Pd/Ru catalytic cycle follows the mechanism proposed by Sanford *et al.*²¹ The increased yield in the visible-light photocatalysed Pd-mediated protocol is attributed to the transformation step leading to the formation of the Pd(IV) complex. In the presence of the photocatalyst the reaction proceeds via a low-energy SET pathway and avoids the high-energy oxidative addition step in the Pd-only catalysed reaction pathway.

Chapter 4 aims to extend the arylation/nuisance effect chemistry to a wider scope of privileged structures with different nucleophiles for application in medicinal chemistry library generation.

3.4 Experimental details for Chapter 3

General Information

General experimental details are provided in Chapter 2.4.

3.4.1 4-Methoxybenzenediazonium tetrafluoroborate (**3.9**)

A stirred suspension of 4-fluorobenzenediazonium tetrafluoroborate (0.10 g, 0.48 mmol) in methanol (2 mL) was heated at reflux for 1 hour. The reaction was allowed to cool to ambient temperature and concentrated under reduced pressure. The residue was precipitated by the addition of diethyl ether and collected by filtration, affording the titled product as a white solid (0.090 g, 85%). The spectral data were concurrent with those reported.^{43,44}

3.4.2 4-Ethoxybenzenediazonium tetrafluoroborate (**3.10**)

The reaction was conducted by the same procedure as for **3.9**, but ethanol (2 mL) was used instead of methanol and heated at 70°C for 1 hour. The titled product was obtained as a white solid (0.071 g, 63%). The spectral data were concurrent with those reported.⁴⁵

3.4.3 2-Methoxybenzenediazonium tetrafluoroborate

The reaction was conducted by the same procedure as for **3.9** but 2-fluorobenzenediazonium tetrafluoroborate (0.10, 0.48 mmol) was used instead. The titled product was obtained as a white solid (0.073 g, 72%). The spectral data were concurrent with those reported.⁴⁵

3.4.4 5-(2'-Fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**3.1**); 5-(2'-methoxybiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**3.4**)

5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.070 g, 0.3 mmol), 2-fluorobenzenediazonium tetrafluoroborate (0.25 g, 1.20 mmol) and palladium (II) acetate (0.0067 g, 0.03 mmol), tris(2,2'-bipyridyl)ruthenium (II) chloride hexahydrate (0.0056 g, 0.0075 mmol) were suspended in degassed, anhydrous methanol (5 mL). Two fluorescent light bulbs (26 W) were placed on either side of the reaction vessel and the reaction mixture was heated at reflux for 4 hours. The reaction was allowed to cool to ambient

temperature, diluted with ethyl acetate (50 mL), washed with water (20 mL) and aqueous sodium sulphite (10%, 35 mL x 2). The layers were separated and the combined aqueous layers were extracted with ethyl acetate (50 mL). Thereafter the combined organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting crude material was purified by reversed phase chromatography (water/acetonitrile with 0.1% formic acid, 5 min at 0%, 30%-90%). Starting material, 5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.014 g, 0.06 mmol). Two products were generated; **3.1** was obtained as a white solid (0.022 g, 28%) and **3.4** was obtained as a white solid (0.030 g, 37%). **3a**: The spectral data were concurrent with those reported.¹⁷

3.4: ¹H-NMR (500 MHz) CDCl₃: δ = 7.98 (s, **NH**, 1H), 7.68 (d, ³*J*_{HH} = 7.0 Hz, **ArH**, 1H), 7.52 – 7.42 (m, **ArH**, 2H), 7.28 (d, ³*J*_{HH} = 8.0 Hz, **ArH**, 1H), 7.19 – 7.12 (m, **ArH**, 1H), 7.06 – 6.98 (m, **ArH**, 2H), 6.90 – 6.83 (m, **ArH**, 1H), 6.80 (d, ³*J*_{HH} = 7.5 Hz, **ArH**, 1H), 6.69 – 6.60 (m, **ArH**, 2H), 6.52 (d, ³*J*_{HH} = 8.0 Hz, **ArH**, 1H), 4.22 (s, **COCH₂**, 2H), 3.51 (s, **O-CH₃**, 3H).

¹³C-NMR (126 MHz) CDCl₃: δ = 173.1(**C=O**), 171.1 (**C=N**), 156.1 (**ArC**), 140.8 (**ArC**), 139.0 (**ArC**), 137.4 (**ArC**), 131.3 (**ArC**), 131.5 (**ArC**), 131.4 (**ArC**), 131.1 (**ArC**), 130.3 (**ArC**), 129.8 (**ArC**), 129.6 (**ArC**), 129.3 (**ArC**), 128.9 (**ArC**), 127.7 (**ArC**), 123.3 (**ArC**), 120.3 (**ArC**), 120.2 (**ArC**), 110.0 (**ArC**), 56.7 (**COCH₂**), 55.3 (**O-CH₃**).

HRMS-ESI (m/z) calculated for C₂₂H₁₈FN₂O₂ [**+H**]⁺: 343.1441, found: 343.1446. LCMS purity (UV) = 96 %, tR 10.63 min.

3.4.5 5-(3'-Fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**3.2**)

The reaction was conducted on a 0.20 mmol scale by the same procedure as for **3.1/3.4** but 3-fluorobenzenediazonium tetrafluoroborate (0.17 g, 0.8 mmol) was used instead of 2-fluorobenzenediazonium tetrafluoroborate. Starting material, 5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.010 g, 0.042 mmol) and **3.2** was obtained as a white solid (0.040 g, 77%). The spectral data were concurrent with those reported.¹⁷

3.4.6 5-(4'-Fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**3.3**); 5-(4'-Methoxybiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**3.6**)

This reaction was conducted on a 0.42 mmol scale by the same procedure as **3.1/3.4** and 4-fluorobenzenediazonium tetrafluoroborate (0.35 g, 1.67 mmol) was used instead of 2-fluorobenzenediazonium tetrafluoroborate. Starting material, 5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.015 g, 0.06 mmol) and the reaction generated two products; **3.3** was obtained as a white solid (0.053 g, 45%) and **3.6** was obtained as a white solid (0.038 g, 32%).

3.3: $^1\text{H-NMR}$ (500 MHz) DMSO- d_6 : δ = 10.39 (s, 1H), 7.60 – 7.55 (m, 1H), 7.55 – 7.52 (m, 1H), 7.50 (dd, J = 7.4, 1.4 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.21 – 7.17 (m, 1H), 6.92 – 6.86 (m, 4H), 6.83 – 6.77 (m, 2H), 6.69 (dd, J = 7.9, 1.5 Hz, 1H), 4.03 (s, COCH₂, 2H).

$^{13}\text{C-NMR}$ (126 MHz) DMSO- D_6 : δ = 172.1 (C=O), 169.7 (C=N), 161.5 (d, $^1J_{\text{FC}}$ = 244.0 Hz, ArC), 140.4 (ArC), 139.8 (ArC), 139.2 (ArC), 136.9 (ArC), 131.5 (ArC), 130.4 (ArC), 130.5 (d, $^3J_{\text{FC}}$ = 7.5 Hz, 2 x ArC), 130.2 (ArC), 130.1 (ArC), 129.3 (ArC), 128.3 (ArC), 127.8 (ArC), 122.7 (ArC), 120.7 (ArC), 114.9 (d, $^2J_{\text{FC}}$ = 22.0 Hz, 2 x ArC), 57.3 (COCH₂).

HRMS-ESI (m/z) calculated for C₂₁H₁₅FN₂O [$+H$]⁺: 331.1241, found: 331.1244. LCMS purity (UV) = 92%, tR 11.16 min. **3.4:** The spectral data were concurrent with those reported.

3.4.7 5-(4'-Ethoxybiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**3.7**)

The same method as that of **3.1/3.4** was used but ethanol (5 mL) was used as the solvent instead of methanol. Starting material, 5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.020 g, 0.085 mmol). Two products were generated, the titled product was obtained as a white solid (0.043 g, 39%) and Product **3.7** was obtained as a white solid (0.026 g, 22%).

3.7: ^1H -NMR (500 MHz) CDCl_3 : δ = 8.20 (s, **NH**, 1H), 7.68 (d, $^3J_{\text{HH}}$ = 7.5 Hz, **ArH**, 1H), 7.57 – 7.38 (m, **ArH**, 2H), 7.28 (d, $^3J_{\text{HH}}$ = 7.5 Hz, **ArH**, 1H), 7.15 (pt, $^3J_{\text{HH}}$ = 7.5 Hz, **ArH**, 1H), 6.91 – 6.81 (m, **ArH**, 4H), 6.69 (d, $^3J_{\text{HH}}$ = 8.0 Hz, **ArH**, 1H), 6.60 (d, $^3J_{\text{HH}}$ = 8.0 Hz, **ArH**, 2H), 4.29 (s, **COCH₂**, 2H), 3.94 (q, $^3J_{\text{HH}}$ = 7.0 Hz, **O-CH₂CH₃**, 2H), 1.36 (t, $^3J_{\text{HH}}$ = 7.0 Hz, **O-CH₂CH₃**, 3H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 173.2 (**C=O**), 170.7(**C=N**), 157.8 (**ArC**), 141.7 (**ArC**), 139.5 (**ArC**), 137.3 (**ArC**), 133.2 (**ArC**), 131.1 (**ArC**), 130.1 (**ArC**), 129.9 (**ArC**), 129.7 (**ArC**), 129.8 (2 x **ArC**), 129.5 (**ArC**), 129.1 (**ArC**), 128.1 (**ArC**), 126.9 (**ArC**), 123.1 (**ArC**), 113.8 (2 x **ArC**), 63.5 (**O-CH₂CH₃**), 56.5 (**COCH₂**), 14.8 (**O-CH₂CH₃**).

HRMS-ESI (m/z) calculated for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$ [$+\text{Na}$] $^+$: 379.1417, found: 379.1419. LCMS purity (UV) = 87 %, tR 10.89 min.

3.4.8 5-Phenyl-2-yl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**3.11**)

The reaction was conducted by the same procedure as for **3.1/3.4** but benzenediazonium tetrafluoroborate (0.23 g, 1.20 mmol) was used instead of 2-fluorobenzenediazonium tetrafluoroborate. Starting material, 5-Phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was recovered (0.016 g, 0.067 mmol) and **3.11** was obtained as a white solid (0.043 g, 60%). All Spectral data were concurrent with those reported.¹⁷

3.4.9 5-(4'-Methoxybiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**3.12**)

The reaction was conducted on a 0.32 mmol scale by the same procedure as for **3.1/3.4** but 4-methoxybenzenediazonium tetrafluoroborate (0.28 g, 1.28 mmol) was used instead of 2-fluorobenzenediazonium tetrafluoroborate. Starting material, 5-Phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was recovered (0.015 g, 0.063 mmol) and **3.12** was obtained as a white solid (0.048 g, 54%). All Spectral data were concurrent with those reported.

3.4.10 5-(4'-Nitrobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**3.13**)

The reaction was conducted on a 0.45 mmol scale by the same procedure as for **3.1/3.4** but 4-nitrobenzenediazonium tetrafluoroborate (0.43 g, 1.80 mmol) was used instead.

Starting material, 5-Phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was recovered (0.020 g, 0.085 mmol) and **3.13** was obtained as a white solid (0.093 g, 71%).

¹H-NMR (500 MHz) CDCl₃: δ = 8.78 (s, 1H), 7.94 (dd, ³*J*_{HH} = 8.5, 1.5 Hz, 2H), 7.78 – 7.72 (m, 1H), 7.60 – 7.52 (m, 2H), 7.34 – 7.28 (m, 1H), 7.22 – 7.13 (m, 3H), 6.90 – 6.83 (m, 2H), 6.72 (d, ³*J*_{HH} = 8.0 Hz, 1H), 4.31 (s, COCH₂, 2H).).

¹³C-NMR (126 MHz) CDCl₃: δ = 172.1 (C=O), 170.6 (C=N), 147.4 (ArC), 146.6 (ArC), 139.7 (ArC), 139.6 (ArC), 137.5 (ArC), 131.7 (ArC), 130.4 (ArC), 129.9 (ArC), 129.8 (ArC), 129.6 (ArC), 129.5 (ArC x 2), 128.7 (ArC), 128.6 (ArC), 123.3 (ArC), 122.7 (ArC x 2), 120.1 (ArC), 56.5 (COCH₂).

HRMS-ESI (m/z) calculated for C₂₁H₁₅N₃O₃ [+H]⁺: 358.1186, found: 358.1191. Elemental Analysis: Calculated for C₂₁H₁₅N₃O₃ (%): C, 70.58, H, 4.23, N, 11.76, found: C, 70.41, H, 4.23, N, 11.60.

3.4.11 5-(4'-Bromobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**3.14**)

The reaction was conducted on a 0.25 mmol scale by the same procedure as for **3.1/3.4** but 4-bromobenzenediazonium tetrafluoroborate (0.27 g, 1.0 mmol) was used instead. Starting material, 5-Phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was recovered (0.012 g, 0.051 mmol) and **3.14** was obtained as a white solid (0.051 g, 65%).

¹H-NMR (500 MHz) DMSO-d₆: δ = 10.44 (s, 1H), 7.56 (pt, ³*J*_{HH} = 8.0 Hz, 2H), 7.54 – 7.48 (m, 1H), 7.34 (d, ³*J*_{HH} = 8.0 Hz, 1H), 7.28 (d, ³*J*_{HH} = 8.0 Hz, 2H), 7.23 (pt, ³*J*_{HH} = 7.5 Hz, 1H), 6.87 (dd, *J* = 8.0, 5.9 Hz, 3H), 6.82 (pt, ³*J*_{HH} = 7.5 Hz, 1H), 6.73 (d, ³*J*_{HH} = 8.0 Hz, 1H), 4.05 (s, COCH₂, 2H).

¹³C-NMR (126 MHz) DMSO-d₆: δ = 171.9 (C=O), 169.8 (C=N), 140.2 (ArC), 139.8 (ArC), 139.6 (ArC), 139.3 (ArC), 131.5 (ArC), 131.1 (ArC), 131.0 (ArC x 2), 130.6 (ArC x 2), 130.3 (ArC), 130.2 (ArC), 130.1 (ArC), 129.5 (ArC), 128.2 (ArC), 128.1 (ArC), 122.7 (ArC), 120.7 (ArC), 56.7 (COCH₂).

HRMS-ESI (m/z) calculated for $C_{21}H_{15}BrN_2O$ $[+H]^+$: 391.0441, found: 391.0449. LCMS purity (UV) = 95 %, tR 14.56 min.

3.4.12 5-(3'-Trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**3.15**); 5-(3,3'-bistrifluoromethylbiphenyl-2,6-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**3.16**)

The reaction was conducted on a 0.39 mmol scale by the same procedure as for **3.1/3.4** but 3-trifluoromethylbenzenediazonium tetrafluoroborate (0.41 g, 1.56 mmol) was used instead. **3.15** was obtained as a brown solid (0.094 g, 64%) and the bisarylated product, **3.16**, was obtained as a brown solid (0.061 g, 30%). **3.15**: All spectral data were concurrent with those reported.¹⁷

3.16: 1H -NMR (500 MHz) DMSO- d_6 : δ = 10.01 (s, 1H), 7.66 (pt, $^3J_{HH}$ = 7.5 Hz, 1H), 7.55 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.50 (d, $^3J_{HH}$ = 7.5 Hz, 2H), 7.45 (pt, $^3J_{HH}$ = 7.5 Hz, 2H), 7.41 – 7.36 (m, 4H), 7.22 – 7.18 (m, 1H), 6.96 – 6.89 (m, 2H), 6.75 (d, J = 8.0 Hz, 1H), 3.65 (s, $COCH_2$, 2H).

^{13}C -NMR (126 MHz) $CDCl_3$: δ = 170.4 (C=O), 169.6 (C=N), 141.4 (ArC), 141.0 (ArC), 138.1 (ArC), 137.4 (ArC), 132.4 (ArC x 2), 131.7 (ArC), 130.1 (q, $^2J_{FC}$, 33 Hz, ArC x 2), 129.8 (ArC x 2), 129.4 (ArC x 2), 129.3 (ArC x 2), 128.7 (ArC), 128.2 (ArC x 2), 125.8 (q, $^3J_{FC}$, 3.5 Hz, ArC x 2), 123.9 (q, $^3J_{FC}$, 272.0 Hz ArC x 2), 123.7 (q, $^3J_{FC}$, 3.5 Hz, ArC x 2), 123.4 (ArC), 120.2 (ArC), 55.7 ($COCH_2$).

HRMS-ESI (m/z) calculated for $C_{29}H_{18}F_6NO_2$ $[+H]^+$: 525.1396, found: 525.1402. LCMS purity (UV) = 98 %, tR 22.50 min.

3.5 Computational Details

Density functional theory (DFT) calculations were performed at the ω B97XD/6-311++G(2df,2p)[SDD]/PBE/6-31+G(d,p)[SDD] level of theory, using the Gaussian09 program.⁴⁶ The Pople basis sets were used on all atoms except Pd and Ru for which the SDD effective core potentials were used.⁴⁷ The PBE functional⁴⁸ was used for the

geometry optimisation and frequency analysis as it combines good accuracy for Pd complexes with computational speed.^{49,50} The long-range corrected hybrid functional ω B97XD,⁵¹ which includes empirical dispersion corrections, was used for energies to ensure accurate energetics.^{52–55} Methanol solvent energy corrections were applied using the conductor-like polarisable continuum model (CPCM).^{56,57} All stationary states were verified as minima or transition states by the absence or presence, respectively, of a single imaginary vibrational frequency. Eigenvector following was used to ensure transition states connected the desired minima.

The Gibbs free energy barrier for single electron transfer (SET), ΔG_{ET}^\ddagger , was calculated using the following equation from Marcus and Savéant theory:^{34–38}

$$\Delta G_{ET}^\ddagger = \Delta G_0^\ddagger \left[1 + \frac{\Delta G_r}{4\Delta G_0^\ddagger} \right]^2 \quad (1)$$

Here ΔG_r is the reaction energy for the electron transfer step and ΔG_0^\ddagger is the intrinsic barrier, which can be calculated as:

$$\Delta G_0^\ddagger = \frac{\lambda}{4} \quad (2)$$

In Eq. (2), λ is the reorganisation energy and consists of the inner reorganisation energy of the reactants, λ_i , and the solvent reorganisation energy, λ_o . For outer-sphere electron transfer as in the present case, λ_i is assumed to be zero (following literature precedents)⁵⁸ thus λ is equal to λ_o .

The reaction energy for the electron transfer step ΔG_r is calculated as the energy of the reaction: Pd(III)-complex + [Ru(bpy₃)]³⁺ → Pd(IV)-complex + [Ru(bpy₃)]²⁺ (i.e. **Int5**(SET) to **Int7**, Scheme 5). The energy for this step is -83.4 kJ mol⁻¹.

The reorganisation energy $\lambda = \lambda_o$ is calculated using the following equation:⁵⁹

$$\lambda_o = \frac{N_A e^2}{4\pi\epsilon_0} \left(\frac{1}{\epsilon_{op}} - \frac{1}{\epsilon_s} \right) \left(\frac{1}{2r_1} + \frac{1}{2r_2} - \frac{1}{R} \right) \quad (3)$$

Where N_A is the Avogadro constant ($6.022 \times 10^{23} \text{ mol}^{-1}$), e is the electronic charge ($1.602 \times 10^{-19} \text{ C}$), ϵ_0 is the vacuum permittivity ($8.854 \times 10^{-12} \text{ J}^{-1} \text{ C}^2 \text{ m}^{-1}$) and, ϵ_{op} and ϵ_s are the optical and static dielectric constant for solvent, respectively. For methanol, ϵ_{op} is 1.76 and ϵ_s is 32.613. r_1 , r_2 and R are the hard sphere radii of the donor, the acceptor, and their sum. In this work, the hard sphere radii approximation of $[\text{Ru}(\text{bpy})_3]^{3+}$ and the Pd(III)-complex (**Int5(SET)**) were calculated using the VOLUME keyword in Gaussian09. The calculated $[\text{Ru}(\text{bpy})_3]^{3+}$ radius is 6.18 Å and the calculated Pd(III)-complex radius is 6.47 Å. Using these values in Eq. (3) gives $\lambda_o = 59.1 \text{ kJ mol}^{-1}$, and hence $\Delta G_0^\ddagger = 14.8 \text{ kJ mol}^{-1}$. Substituting these values for ΔG_0^\ddagger and ΔG_r in Eq. (1), provides a SET barrier, $\Delta G_{ET}^\ddagger = 2.5 \text{ kJ mol}^{-1}$.

3.6 References

- 1 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.
- 2 M. A. J. Duncton, C. Punta, F. Minisci, F. Minisci, F. Fontana, E. Vismara, F. Minisci, E. Vismara, F. Fontana, D. C. Harrowven, B. J. Sutton, D. C. Harrowven, B. J. Sutton, S. Coulton, D. C. Harrowven, B. J. Sutton, S. Coulton, R. W. Bowman, J. M. D. Storey, M. Gomberg, W. E. Bachmann, R. Möhlau, R. Berger, R. Möhlau, R. Berger, L. K. Dyll, K. H. Pausacker, B. M. Lynch, H. S. Chang, B. M. Lynch, H. S. Chang, H. J. M. Dou, B. M. Lynch, H. J. M. Dou, H. J. M. Dou, B. M. Lynch, H. J. M. Dou, B. M. Lynch, R. D. Brown, R. D. Brown, M. L. Heffernan, F. Minisci, R. Galli, M. Cecere, V. Malatesta, T. Caronna, P. Ertle, S. Jelfs, J. Mühlbacher, A. Schuffenhauer, P. Selzer, H. B. Broughton, I. A. Watson, X. Q. Lewell, A. C. Jones, C. L. Bruce, G. Harper, M. M. Jones, I. M. Mclay, J. Bradshaw, S. Gibson, R. McGuire, D. C. Rees, G. W. Bemis, M. A. Murcko, F. Minisci, R. Bernadi, F. Bertini, R. Galli, M. Perchinunno, M. A. J. Duncton, M. A. Estiarte, M. Cox, D. J. R. O'Mahony, R. J. Johnson, W. T. Edwards, M. G. Kelly, S. Basili, S. Moro, D. Kim, N. Lee, S. Sawada, S. Okijima, R. Aiyama, K. Nokata, T. Furuta, T. Yokokura, E. Sugino, K. Yamaguchi, T. Miyasaka, S. Sawada, K. Nokata, H. Nagata, T. Furuta, T. Yokokura, T. Miyasaka, S. Sawada, S. Matsuoka, K. Nokata, H. Nagata, T. Furuta, T. Yokokura, T. Miyasaka, S. K. Ahn, N. S. Choi, B. S. Jeong, K. K. Kim, D. J. Journ, J. K. Kim, S. J. Lee, J. W. Kim, C. I. Hong, S.

- Jew, S. M. Apana, L. W. Anderson, M. S. Berridge, Z.-F. Xie, K. Ootsu, H. Akimoto, M. Li, W. Jin, C. Jiang, W. Tang, T. You, L. Lou, S. T. Liew, L.-X. Yang, R. Jain, L. A. Cohen, N. A. El-Kadi, M. M. King, C. G. Begg, M. R. Grimmett, L. Yu-Man, S. Narayanan, S. Vangapandu, R. Jain, N. Kaur, V. Monga, R. Jain, N. Kaur, X. Lu, M. C. Gershengorn, R. Jain, N. Kaur, V. Monga, J. S. Josan, X. Lu, M. C. Gershengorn, R. Jain, N. Kaur, V. Onga, X. Lu, M. C. Gershengorn, R. Jain, V. Monga, C. L. Meena, N. Kaur, S. Kumar, C. Pawar, S. S. Sharma, R. Jain, K. B. Hansen, S. A. Springfield, R. Desmond, P. N. Devine, E. J. J. Garbowski, P. J. Reider, R. Jain, B. Vaitilingam, A. Nayyar, P. B. Palde, S. Vangapandu, M. Jain, R. Jain, S. Kaur, P. P. Singh, B. Vaitilingam, A. Nayyar, P. P. Palde, V. Monga, R. Jain, S. Kaur, P. P. Singh, A. Nayyar, V. Monga, A. Malde, E. Coutinho, R. Jain, A. Koul, E. Arnoult, N. Lounis, J. Guillemont, K. Andries, C. Dye, B. G. Williams, R. W. Carling, A. Madin, A. Guiblin, M. G. N. Russell, K. W. Moore, A. Mitchinson, B. Sohal, A. Pike, S. M. Cook, I. C. Regan, R. M. McKernan, K. Quirk, P. Ferris, G. Marshall, S. A. Thompson, K. A. Wafford, G. R. Dawson, J. R. Atack, T. Harrison, J. L. Castro, L. J. Street, C. A. Lipinski, J. L. LaMattina, L. A. Hohnke, P. B. Palde, P. C. Gareiss, B. J. Miller, P. B. Palde, B. R. McNaughton, N. T. Ross, P. C. Gareiss, C. R. Mace, R. C. Spitale, B. L. Miller, D. H. R. Barton, B. Garcia, H. Togo, S. Z. Zard, E. Castagnino, S. Corsano, D. H. R. Barton, S. Z. Zard, C. Fausta, F. Fontana, F. Minisci, G. Pianese, P. Tortoreto, L. Zhao, M. Jarman and E. E. Barrie, *Med. Chem. Commun.*, 2011, **2**, 1135-1161.
- 3 T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900–2936.
 - 4 T. A. Bedell, G. A. B. Hone, D. Valette, J. Q. Yu, H. M. L. Davies and E. J. Sorensen, *Angew. Chem. Int. Ed.*, 2016, **55**, 8270–8274.
 - 5 A. Sharma and J. F. Hartwig, *Nature*, 2015, **517**, 600–604.
 - 6 J. J. Topczewski, P. J. Cabrera, N. I. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220–224.
 - 7 L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885-1898.
 - 8 A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129–133.
 - 9 O. Abdulla, A. D. Clayton, R. A. Faulkner, D. M. Gill, C. R. Rice, S. M. Walton and J. B. Sweeney, *Chem. Eur. J.*, 2017, **23**, 1494–1497.
 - 10 J. P. Barham, M. P. John and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 15482–

- 15487.
- 11 J. He, L. G. Hamann, H. M. L. Davies and R. E. J. Beckwith, *Nat. Commun.* 2015, **6**, 5943-5952, doi:10.1038/ncomms6943.
 - 12 Q. Michaudel, G. Journot, A. Regueiro-Ren, A. Goswami, Z. Guo, T. P. Tully, L. Zou, R. O. Ramabhadran, K. N. Houk and P. S. Baran, *Angew. Chem. Int. Ed.*, 2014, **53**, 12091–12096.
 - 13 D. A. Nagib and D. W. C. Macmillan, *Nature*, 2011, **480**, 224–228.
 - 14 Y. Zhu, M. Bauer and L. Ackermann, *Chem. Eur. J.*, 2015, **21**, 9980–9983.
 - 15 F. Yang, J. Koeller and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 4759–4762.
 - 16 J. Spencer, B. Z. Chowdhry, A. I. Mallet, R. P. Rathnam, T. Adatia, A. Bashall and F. Rominger, *Tetrahedron*, 2008, **64**, 6082–6089.
 - 17 R. Khan, R. Felix, P. D. Kemmitt, S. J. Coles, I. J. Day, G. J. Tizzard and J. Spencer, *Adv. Synth. Catal.*, 2016, **358**, 98–109.
 - 18 E. A. Merritt and B. Olofsson, *Angew. Chemie - Int. Ed.*, 2009, **48**, 9052–9070.
 - 19 M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, *Arkivoc*, 2011, **2011**, 370–409.
 - 20 S. G. Modha and M. F. Greaney, *J. Am. Chem. Soc.*, 2015, **137**, 1416–1419.
 - 21 D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18566–18569.
 - 22 J. Jiang, W. M. Zhang, J. J. Dai, J. Xu and H. J. Xu, *J. Org. Chem.*, 2017, **82**, 3622–3630.
 - 23 M. Majek and A. Jacobi Von Wangelin, *Acc. Chem. Res.*, 2016, **49**, 2316–2327.
 - 24 L. Marzo, I. Ghosh, F. Esteban and B. König, *ACS Catal.*, 2016, **6**, 6780–6784.
 - 25 D. P. Hari, P. Schroll and B. König, *J. Am. Chem. Soc.*, 2012, **134**, 2958–2961.
 - 26 S. J. Coles and P. A. Gale, *Chem. Sci.*, 2012, **3**, 683–689.
 - 27 J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273–412.
 - 28 R. M. M. J. R. Atack, K. A. Wafford, S. J. Tye, S. M. Cook, B. Sohal, A. Pike, C. Sur, D. Melillo, L. Bristow, F. Bromidge, I. Ragan, J. Kerby, L. Street, R. Carling, J. L. Castro, P. Whiting, G. R. Dawson, *J. Pharmacol. Exp. Ther.*, 2006, **316**, 410–422.
 - 29 D. L. Davies, S. M. A. Donald and S. A. Macgregor, *J. Am. Chem. Soc.*, 2005, **127**, 13754–13755.
 - 30 A. Vigalok, O. Uzan, L. J. W. Shimon, Y. Ben-David, J. M. L. Martin and D.

- Milstein, *J. Am. Chem. Soc.*, 1998, **120**, 12539–12544.
- 31 F. Teplý, *Collect. Czechoslov. Chem. Commun.*, 2011, **76**, 859–917.
 - 32 J. R. Khusnutdinova, N. P. Rath and L. M. Mirica, *J. Am. Chem. Soc.*, 2010, **132**, 7303–7305.
 - 33 D. C. Powers and T. Ritter, *Nat. Chem.*, 2009, **1**, 302–309.
 - 34 R. A. Marcus, *J. Chem. Phys.*, 1956, **24**, 966–978.
 - 35 R. A. Marcus, *J. Chem. Phys.*, 1956, **24**, 979–989.
 - 36 J. M. Saveant, *J. Am. Chem. Soc.*, 1987, **109**, 6788–6795.
 - 37 R. A. Marcus, *J. Phys. Chem.*, 1963, **67**, 853–857.
 - 38 R. A. Marcus, *J. Chem. Phys.*, 1956, **24**, 966–978.
 - 39 Q. Zhang, Z. Q. Zhang, Y. Fu and H. Z. Yu, *ACS Catal.*, 2016, **6**, 798–808.
 - 40 A. Ariaferd, C. J. T. Hyland, A. J. Canty, M. Sharma and B. F. Yates, *Inorg. Chem.*, 2011, **50**, 6449–6457.
 - 41 A. J. Canty, A. Ariaferd, M. S. Sanford and B. F. Yates, *Organometallics*, 2013, **32**, 544–555.
 - 42 J. Dupont and M. Pfeffer, *J. Chem. Soc., Dalton Trans.*, 1990, **0**, 3193–3198.
 - 43 P. Hanson, J. R. Jones, B. Taylor, P. H. Walton, W. Timms, *J. Chem. soc., Perkin Trans.*, 2002, **2**, 1135–1150.
 - 44 B. Schmidt, R. Berger and F. Hölder, *Org. Biomol. Chem.*, 2010, **8**, 1406–1414.
 - 45 S. H. Korzeniowski, A. Leopold, J. R. Beadle, M. F. Ahern, W. A. Sheppard, R. K. Khanna and G. W. Gokel, *J. Org. Chem.*, 1981, **46**, 2153–2159.
 - 46 D. J. Frisch, M. J. Trucks, G. W. Schlegel, H. B.; Scuseria, G. E.; Robb, M. A. Cheeseman, J. R. Scalmani, G. Barone, V. Mennucci, B. Petersson, G. A. Nakatsuji, H. Caricato, M. Li, X. Hratchian, H. P. Izmaylov, A. F. Bloino, J. Zheng, G. Sonnenber, *Gaussian, Inc. Wallingford CT*, 2009, 2–3.
 - 47 D. Andrae, U. Häußermann, M. Dolg, H. Stoll and H. Preuß, *Theor. Chem. Accounts Theory, Comput. Model. (Theoretica Chim. Acta)*, 1990, **77**, 123–141.
 - 48 J. P. Perdew, K. Burke and M. Ernzerhof, *Phys. Rev. Lett.*, 1997, **78**, 1396–1396.
 - 49 S. Boonseng, G. W. Roffe, J. Spencer and H. Cox, *Dalton Trans.*, 2015, **44**, 7570–7577.
 - 50 P. Surawatanawong and M. B. Hall, *Organometallics*, 2008, **27**, 6222–6232.
 - 51 J. D. Chai and M. Head-Gordon, *J. Phys. Chem. A*, 2008, **10**, 6615–6620.
 - 52 Y. Minenkov, G. Occhipinti and V. R. Jensen, *J. Phys. Chem. A*, 2009, 11833–11844.

- 53 N. Sieffert and M. Bühl, *Inorg. Chem.*, 2009, **48**, 4622–4624.
- 54 M. L. Laury and A. K. Wilson, *J. Chem. Theory Comput.*, 2013, **9**, 3939–3946.
- 55 Y. Zhao and D. G. Truhlar, *J. Chem. Theory Comput.*, 2011, **7**, 669–676.
- 56 V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995–2001.
- 57 M. Cossi, N. Rega, G. Scalmani and V. Barone, *J. Comput. Chem.*, 2003, **24**, 669–681.
- 58 G. O. Jones, P. Liu, K. N. Houk and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 6205–6213.
- 59 R. A. Marcus and N. Sutin, *BBA Rev. Bioenerg.*, 1985, 811, 265–322.
- 60 Y. L. Ching, M. L. Coote, A. Gennaro and K. Matyjaszewski, *J. Am. Chem. Soc.*, 2008, **130**, 12762–12774.
- 61 R. A. Marcus and N. Sutin, *Biochim. Biophys. Acta. Rev. Bioenerg.*, 1985, **811**, 265–322.

Chapter 4

This Chapter is written in an article style and has not been published elsewhere. Our collaborators at Structural Genomics Consortium (SGC), Oxford, have performed all the X-ray crystallography and are responsible for the preliminary biological results presented in this Chapter.

4.1 Preface

Chapters 2 and 3 have demonstrated the successful use of palladium catalysed C-H activation in synthesising ortho-arylated BZDs. In this Chapter, the C-H activation method is employed for synthesising libraries of 2-phenylpyridines and 1-phenyl-2-pyrrolidinones, which also show promising biological activity towards the NUDT7 α protein (a peroxisomal coenzyme A diphosphatase). Although, the fragments readily bind at the binding pocket of NUDT7 α , the quantitative data for the biological tests are still awaiting.

In the following sections, upon a brief overview of the C-H functionalisation, this chapter highlights different types of C-H activation methodologies such as metal catalysed C-H activations. It includes the use of palladium catalysis in C-H functionalisation, which has been thoroughly used in this project. Subsequently, NUDT7 α is introduced with a discussion of its functions and key roles in biological processes. This is followed by an analysis of the results and a brief conclusion to this Chapter.

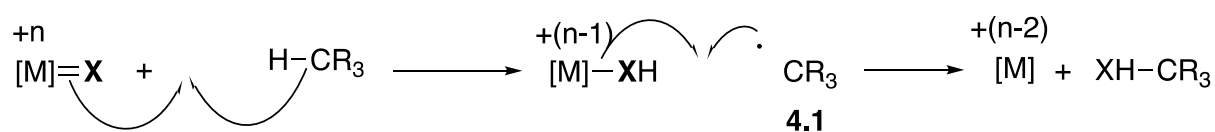
4.2 C-H functionalisation

Most organic molecules are made from non-renewable raw materials which include natural gas and crude oil. Desired organic molecules are derived by breaking and making new C-C bonds by transforming C-H bonds into specific functional groups. Traditionally C-H bond functionalisation is often achieved by initial radical functionalisation or partial aerobic oxidation, which are typically followed by a number of steps facilitating the introduction of the targeted functional groups to construct desired molecules.¹⁻³ This process is known as functional group interconversion strategy and is so profoundly important for organic synthesis, that many organic textbooks contain topics following the sequence of this approach. The typical sequence starts with radical C-H functionalisation (halogens) followed by elimination and substitution, reductions and oxidation as well as carboxyl and carbonyl chemistry. However, this remarkably useful functional group interconversion strategy suffers from a basic disadvantage; it often results in wasteful processes as it involves several steps to convert the unfunctionalised raw material into desired products.⁴

C-H activation with subsequent functionalisation *in situ* offers an approach to introduce substituents into molecules in a one-step synthesis. Product and site-selective C-H functionalisations have been referred to as the “holy grail” of catalysis research.⁵ The high bond dissociation energies (BDEs) of hydrocarbons make them very difficult to break and present great challenges for direct C-H functionalisation. Moreover, C-H bond activation is also kinetically more challenging than C-X bonds, as they do not have suitable lone pairs to coordinate with the catalysts.⁶ Successful C-H functionalisation methods need to surpass a number of critical challenges in addition to cleaving very strong and weakly coordinating bonds. Additionally, the successful catalysts in these processes need to possess the following criteria:

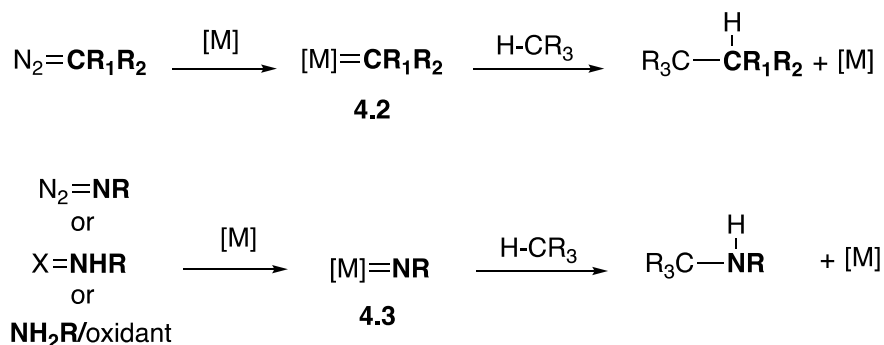
- Show selectivity for a particular kind of C-H bond in a system,
- remain stable and activated in the presence of necessary oxidants, other coordinating functional groups in the product or solvent, and
- be reluctant to further functionalisation *i.e.*, over-oxidation of the products.

Mechanistically, C-H bond functionalisations vary significantly, which may define the types of C-H bonds that can be cleaved and thereby have an influence on selectivity. One such mechanism is the radical rebound mechanism where an H-atom is abstracted followed by radical functionalisation. These mechanisms frequently occur for metal-oxo catalysts and sometimes for functionalisations that progress through metal nitrenoids. Due to the nature of the radical intermediate (**4.1** in Scheme 4.1), selectivity towards weak C-H bonds for functionalisation is often observed in such mechanisms.⁷



Scheme 4.1: Radical rebound mechanism

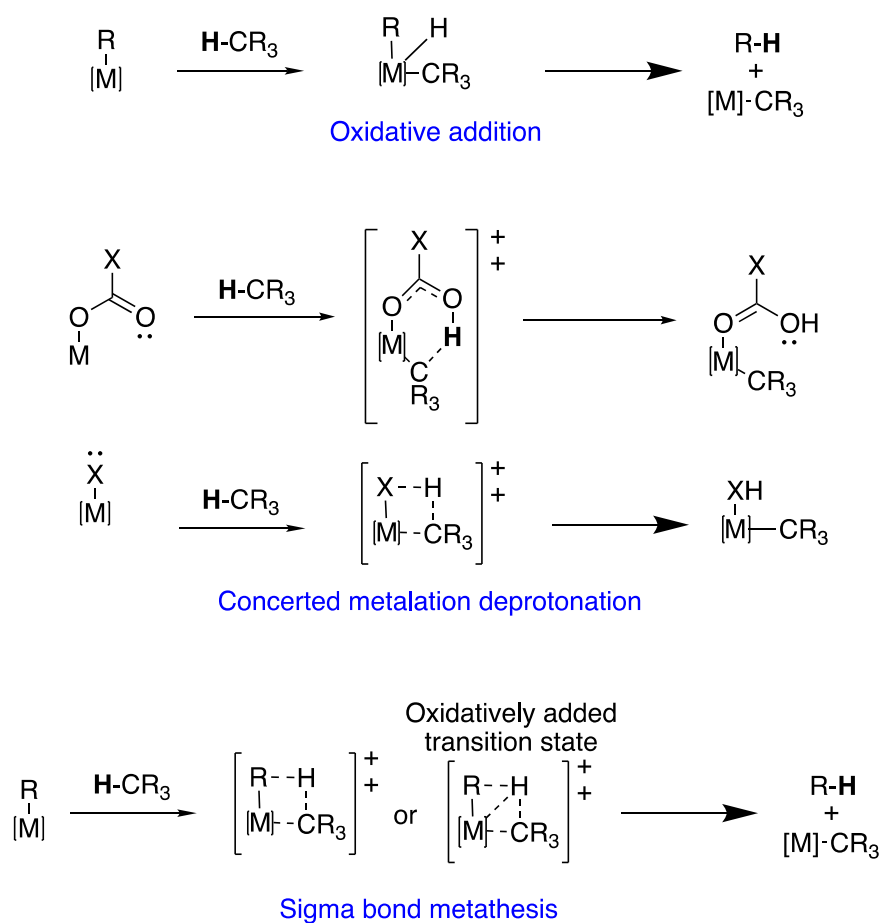
In direct insertions, the unsaturated intermediate (**4.2**, **4.3**) directly attack the C-H bond and form the product in one concerted step and usually proceed through metal nitrenes and carbenes. Although cleaving weak C-H bond is typical for these mechanisms, alkane C-H functionalisations have also been postulated to follow this pathway.^{8,9}



Scheme 4.2: Direct insertion C-H bond activation

Organometallic C-H bond activations proceeding through intermediates with M-C bonds are one of the most common mechanistic pathways for C-H functionalisation. The C-H bond breakage in this pathway may proceed through several distinct mechanisms such as oxidative addition, concerted metallation deprotonation, through a 4- or 6- membered transition state, or sigma bond metathesis, as presented in Scheme 4.3. The specific

mechanism pathway for C-H cleavage generally depends on the metal, its oxidation state and the associated ligands.



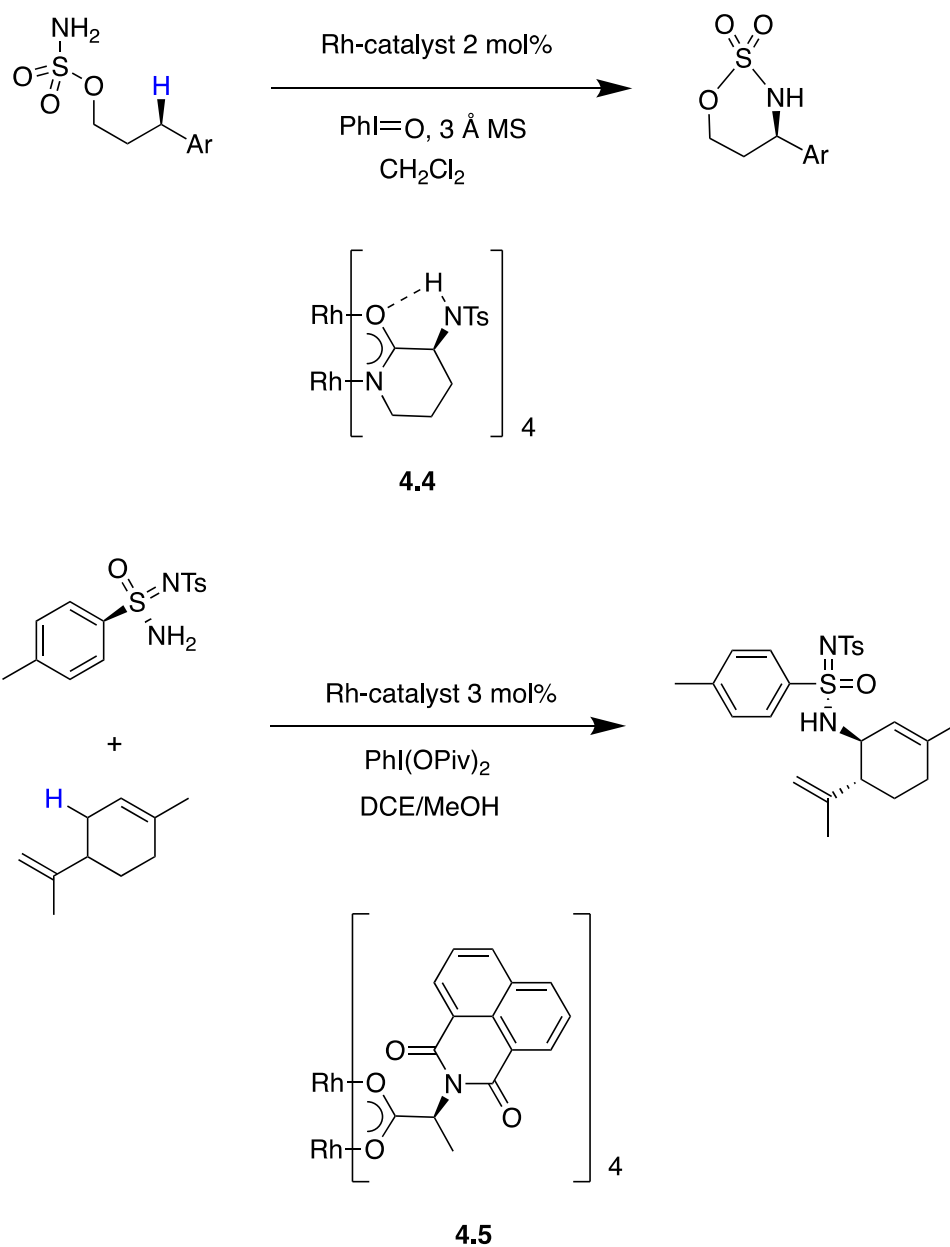
Scheme 4.3: Mechanisms for organometallic C-H bond activation

C-H bond activations, through organometallic intermediates, typically break strong C-H bonds in a molecule. Experimental and computational studies suggest that this particular selectivity is due to the M-C bonds being formed in intermediates, which generally have higher bond energies than corresponding C-H bonds.^{10,11}

Chemists have developed many metal catalyst systems for product and site-selective C-H functionalisation with broad synthetic applications. The following sections highlight some of the metal catalyst systems and their applications.

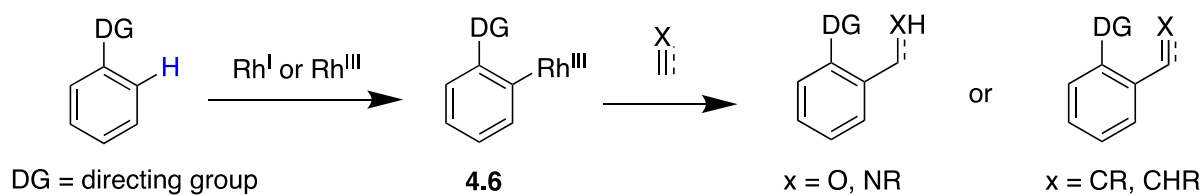
4.2.1 Rhodium (Rh)

Cp*Rh complexes ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) are among the oldest catalyst systems developed for studying the different aspects of organometallic C-H bond activation. One disadvantage of Rh catalysts is their high price. Rhodium is amongst the most expensive precious metals, surpassed only by gold and platinum. Rh catalysts have proven to be extremely successful in C-H activations, particularly in stereoselective C-C and C-N bond formations. Du Bois and co-workers have reported the use of Rh^{II} complexes (containing carboxylate and carboxyamidate ligands) for both intramolecular (**4.4**) and intermolecular (**4.5**) amination with high yields and selectivities (Scheme 4.4).^{12,13}



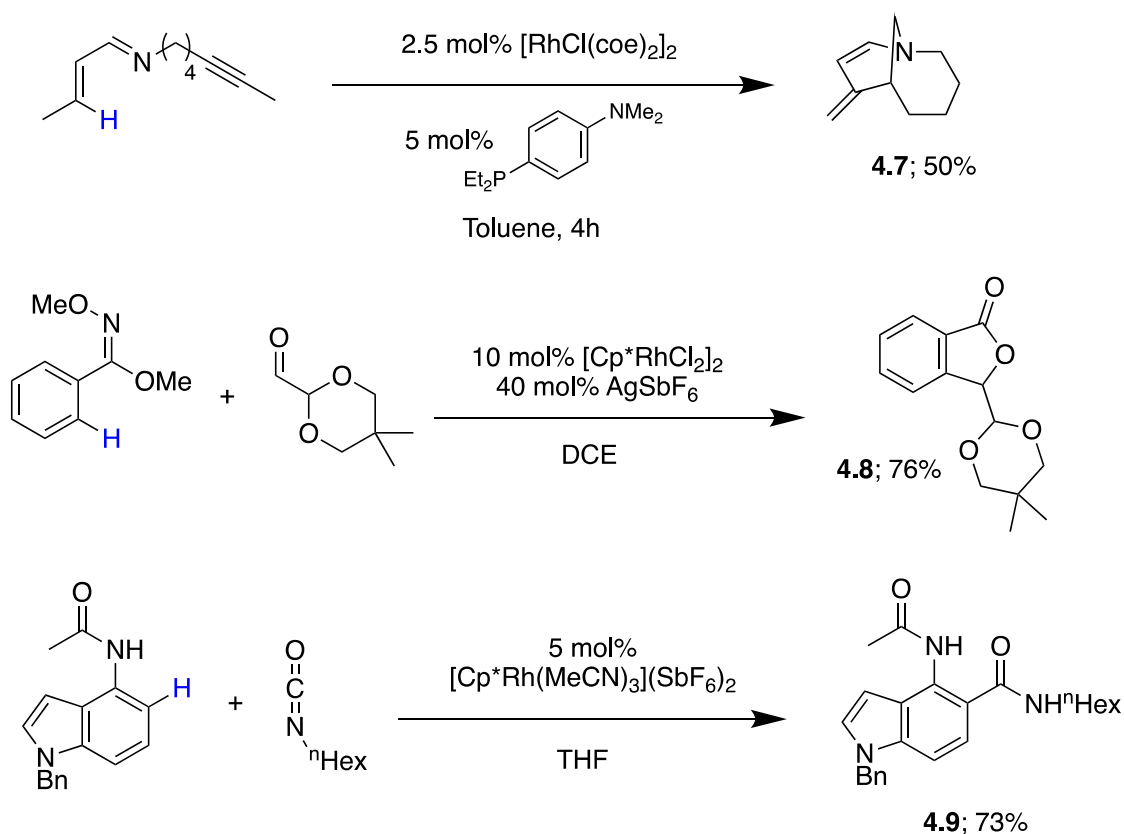
Scheme 4.4: Rh^{II} catalysed intramolecular and intermolecular amination

The mechanism of C-H bond activation by Rh catalysts also depends on its oxidation states. For instance, Rh^I catalysts tend to proceed through oxidative addition since they can readily access the Rh^{III} state, whereas Rh^{III} has been shown to proceed through electrophilic pathways during C-H activation. Ellman *et al.* have reported the use of Rh^I catalyst precursors in addition reactions of C-H bonds through Rh-aryl intermediates, e.g., **4.6** (Scheme 4.5).^{14,15}



Scheme 4.5: Rh-catalysed C-H activation

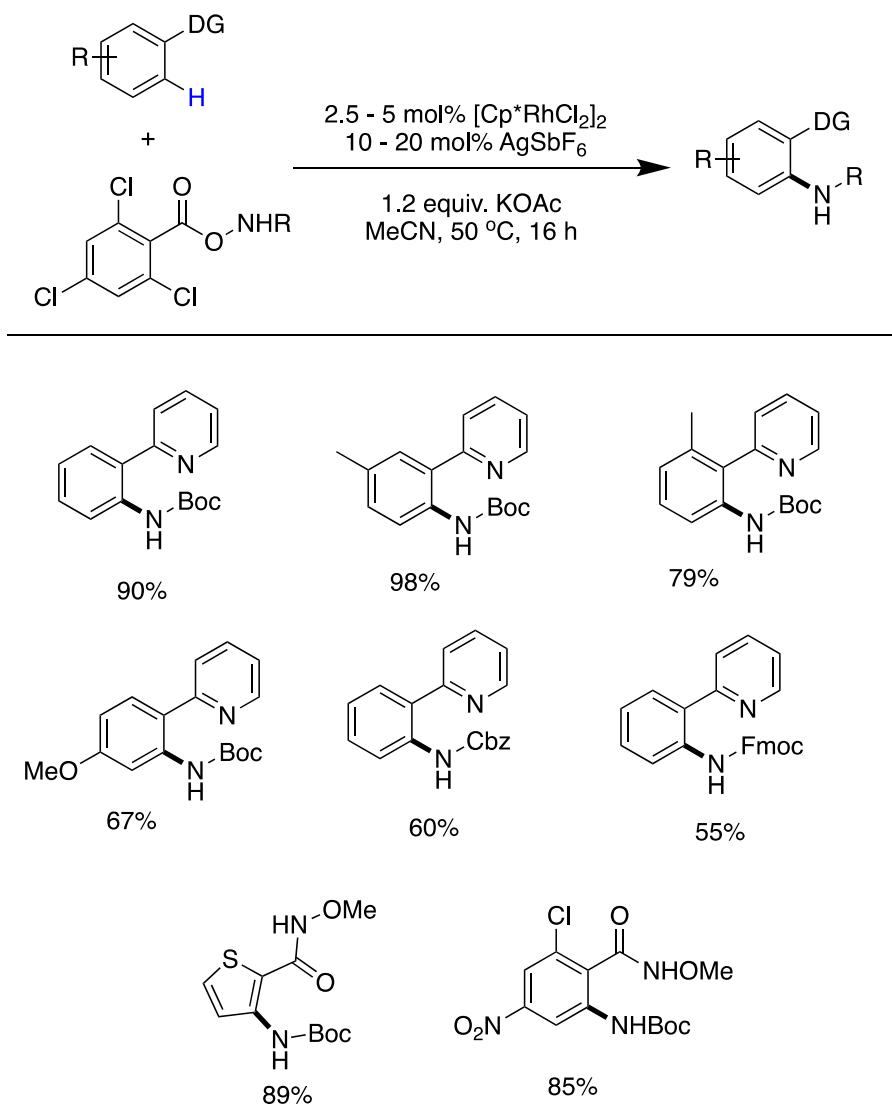
These protocols form new C-C bonds and have been applied in various systems such as olefins, imines, aldehydes and isocyanates. Important heterocycles such as **4.7**, **4.8** and **4.9** can be synthesised using such procedures.^{16–19}



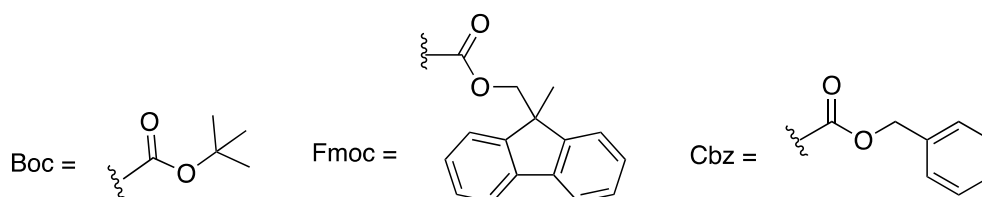
Scheme 4.6: Synthesis of heterocycles by Rh-catalysed C-H functionalisation

A wide range methodologies have been developed for C-H amination in the past decade,^{20–29} many of which are of Rh catalysed protocols. Most of these protocols require substrates with directing groups. Glorius *et al.* have developed mild and convenient

Cp*Rh catalysed amination methodologies using aryloxycarbamates (Scheme 4.7).³⁰ The method shows good tolerance for substituents in ortho, meta and para positions. This protocol also works well with different protecting groups such as Boc (tert-butyloxycarbonyl), Fmoc (fluorenylmethyloxycarbonyl) and Cbz (carboxybenzyl) groups and has variation scope for different substrates as shown in Scheme 4.7.

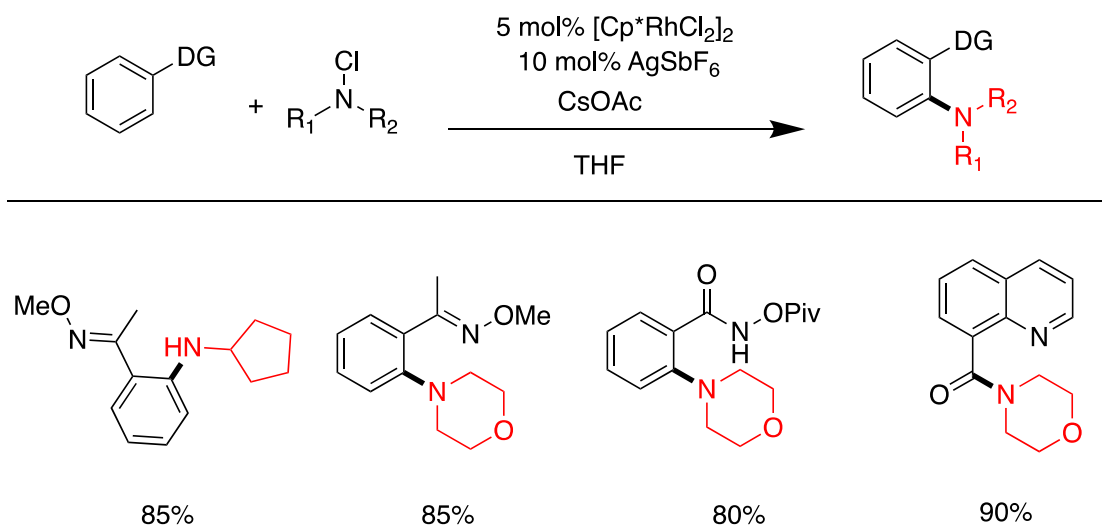


DG = directing group



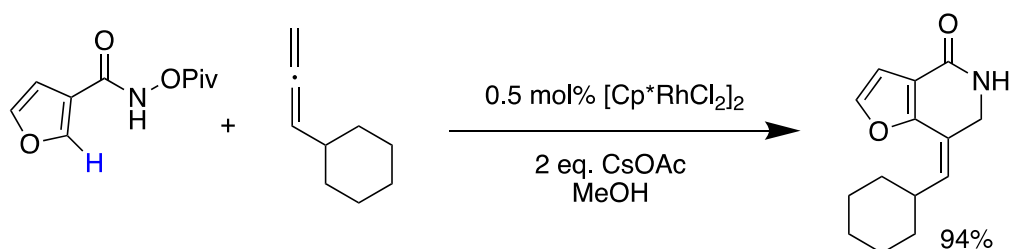
Scheme 4.7: Rhodium catalysed C-H amination

Recently, Yu and Glorius have independently reported the use of secondary and tertiary chloramines as the source of amino groups (Scheme 4.8). Note, a one-pot protocol was developed as the chloramines are unstable and difficult to handle, therefore, the alkyl amines are chlorinated in situ followed by C-H amination.^{31,32}



Scheme 4.8: Rh(III) catalyzed C-H amination with chloramines

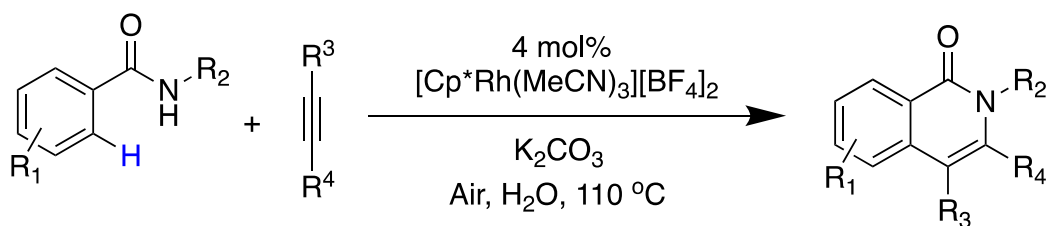
One creative approach in Cp^*Rh catalyzed methodologies is the use of a directing group as an oxidising group simultaneously, known as the oxidising directing group, which are converted under the reaction conditions as shown in Scheme 4.9.^{33–35}



Scheme 4.9: The use of oxidising directing groups in C-H activation

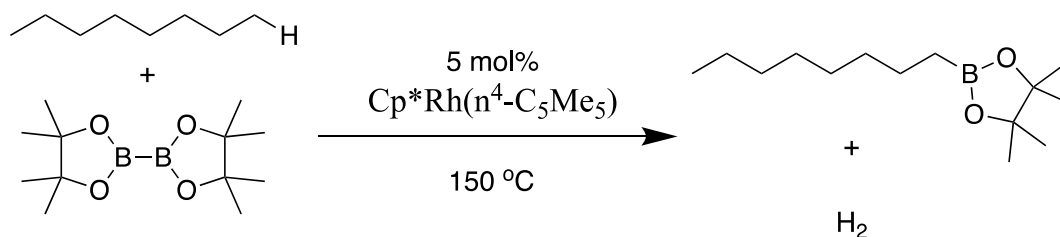
To develop a green approach using Rh(III) catalyst for the highly regioselective synthesis of isoquinolones, Cheng and co-workers have recently reported the use of *N*-alkyl

benzamides and alkynes with air as the oxidant (Scheme 4.10). The best solvent was found to be water in the reaction.³⁶



Scheme 4.12: Regioselective synthesis of isoquinolones

Hartwig *et al.* have developed efficient C-H borylation methods using $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_5\text{Me}_5)$ complexes. These protocols as apparent from Scheme 4.11 enable C-H functionalisations of aliphatic alkanes and are, in fact, highly selective towards functionalisation at primary C-H bonds.^{37,38}

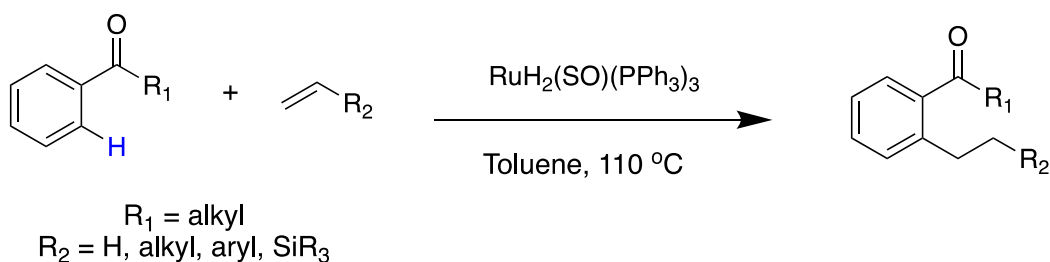


Scheme 4.11: C-H hydroborylation of alkanes

4.2.2 Ruthenium (Ru)

Despite being comparatively less expensive among the precious metals, Ru complexes are one of the less developed catalysts for C-H bond functionalisation. Although there are useful procedures for C-C bond formations using Ru-catalyst systems, these systems are underdeveloped for other types of C-H functionalisation.³⁹ Typical Ru catalysed C-H functionalisations include arylations, allylations, alkylations, alkenylations and acylations.^{40–44} The Murai coupling is an outstanding example of Ru catalysed reactions. This protocol allows the synthesis of alkyl arenes by the C-H arylation of olefins. The advantage of these types of protocols is their ability to use electron-rich alkenes, which

tend to be low yielding substrates in Pd-catalyzed, oxidative Heck reactions (Fujiwara-Moritani).^{45–47}

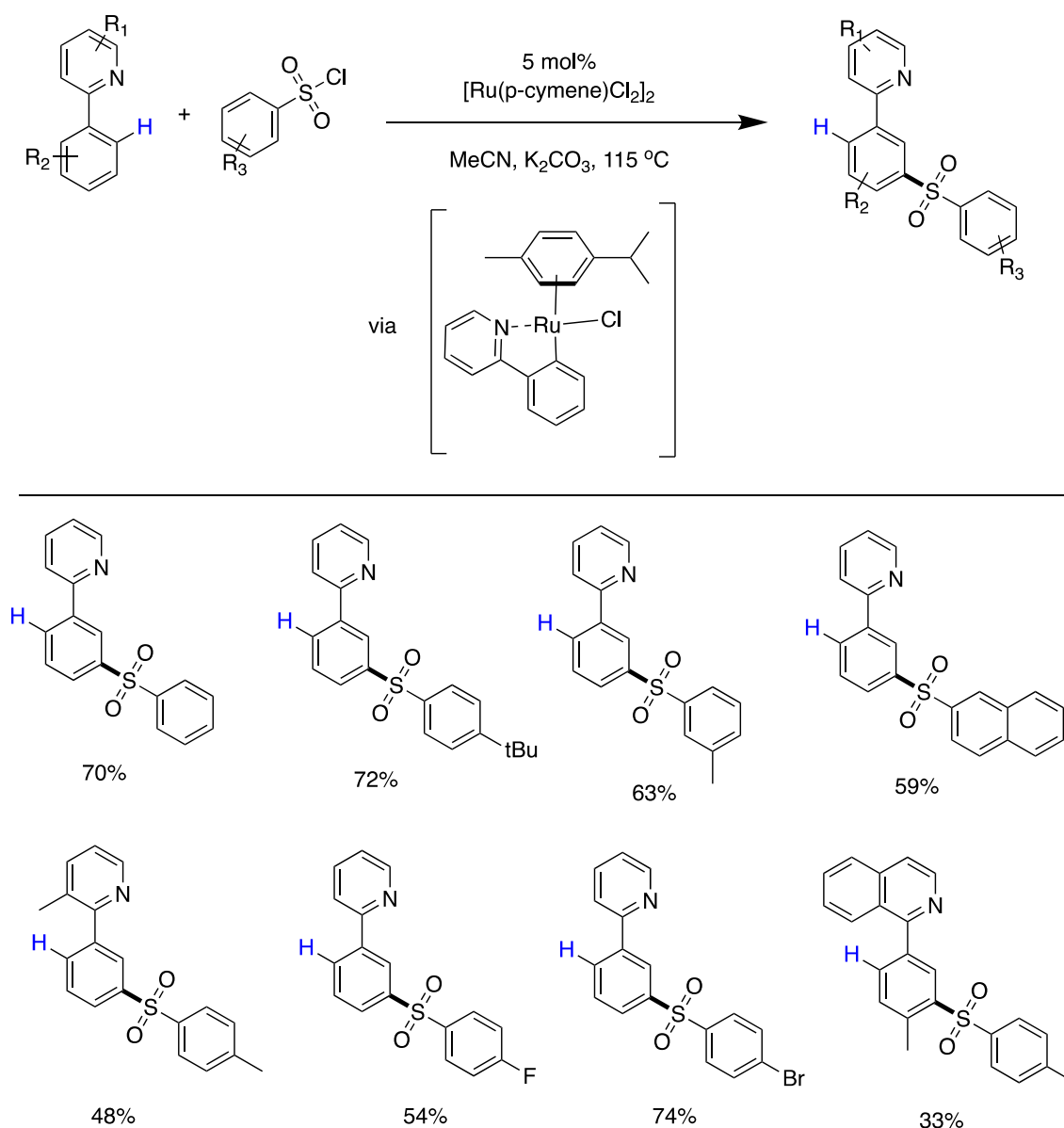


Scheme 4.12: The Murai coupling – formation of alkyl-arenes

There is a higher scope of variation in terms of the directing groups in Ru catalysis as these systems are not restricted to the use of strong electron donating heterocycles. For instance, the use of a ketone as the directing group is common in such reactions and ketones can be directly used for subsequent reactions, which is especially useful for complex molecule syntheses.⁴⁸

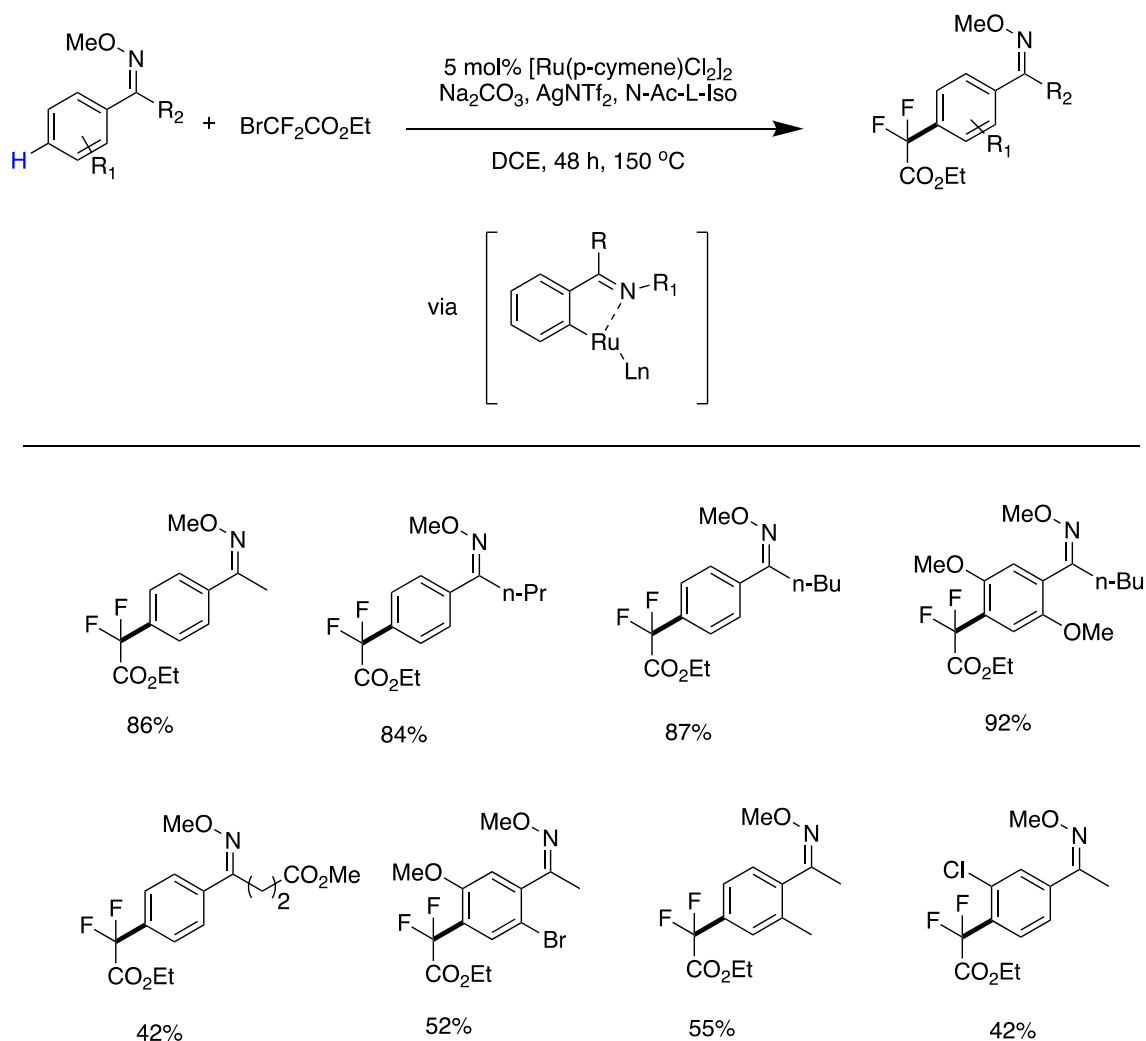
Another remarkable feature of Ru catalysts is their ability to enable C-H functionalisations in the meta-position to the directing group. In these protocols, the electrophilic ligands react with the organometallic intermediate at the para-position of the M-C bond rather than reacting at the M-C bond. These mechanisms are comparable to electrophilic substitutions, where the metal plays the role of an activating, directing group. In a meta-selective C-H sulfonation protocol of 2-phenylpyridines using Ru (II) complexes, developed by Frost and co-workers, the 2-pyridyl group facilitates the formation of stable Ru-C_{aryl} bond that induces the para-directing effect. Subsequently, the electrophilic aromatic substitution occurs with the sulfonyl chloride to install the sulfone at the meta position of the chelating group. Some of the selected examples from this work are shown in Scheme 4.13, with a range of varied functionality and substitution pattern.^{49,50}

Other types of C-H functionalisation such as alkylation, bromination, nitration, benzylation and difluoromethylation have also been reported using meta-selective Ru catalysed C-H functionalisation.^{51–56}



Scheme 4.13: C-H functionalisation at the meta-position

Recently, some para-selective C-H functionalisations have also been reported. For instance, Lan and co-workers have reported a highly para-selective C-H functionalisation protocol, in which they perform difluoromethylation reactions on ketoxime ethers. A computational mechanistic study suggested that the key factor in the para-selectivity of the difluoromethylation is the chelation-assisted cyclo-ruthenation.⁵⁷

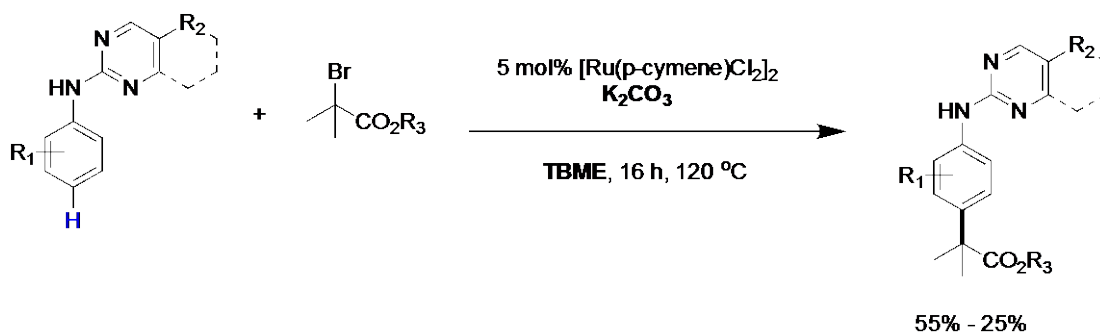


Scheme 4.14: C-H functionalisation at the para-position

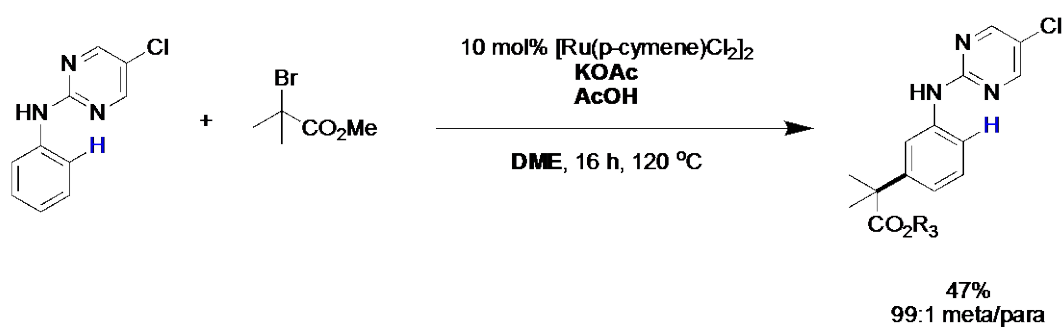
Frost and co-workers reported a para-selective alkylation of aniline derivatives with a pyrimidine auxiliary. The reaction is suggested to occur *via* an N-H activated metallacycle formed *in situ* (Scheme 4.15). Experimental and computational studies indicated that Ru catalyst can undergo cyclometalation by N-H metalation forming a redox active Ru species and enable site-selective radical addition at the para position (the C-H metalation gives rise to the meta product).^{57,58} Interestingly, changing a few reaction parameters of this protocol highly favoured the formation of *meta*-selective products using identical starting material and coupling partner. The meta-selective C-H alkylation was achieved by a change of solvent and base. It was proposed that the N-H cyclometalation was favoured by carbonate bases (K_2CO_3) forming a para-functionalised

product and the use of acetate bases (KOAc) favoured the ortho-C-H cyclometalation to yield meta-functionalised products.

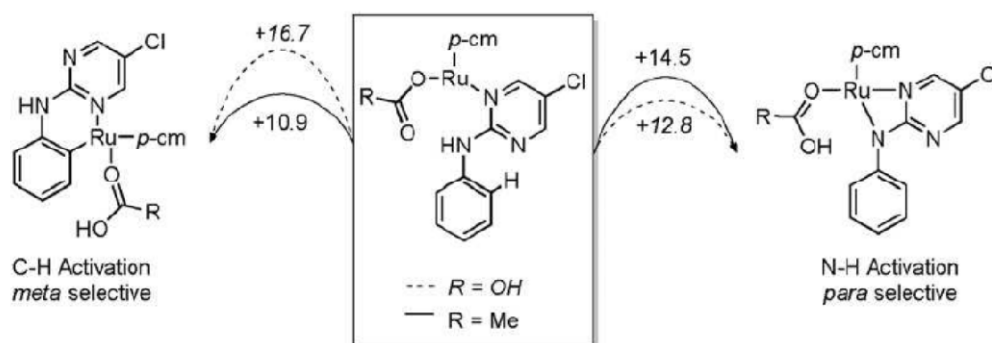
Para-selective C-H alkylation



Meta-selective C-H alkylation



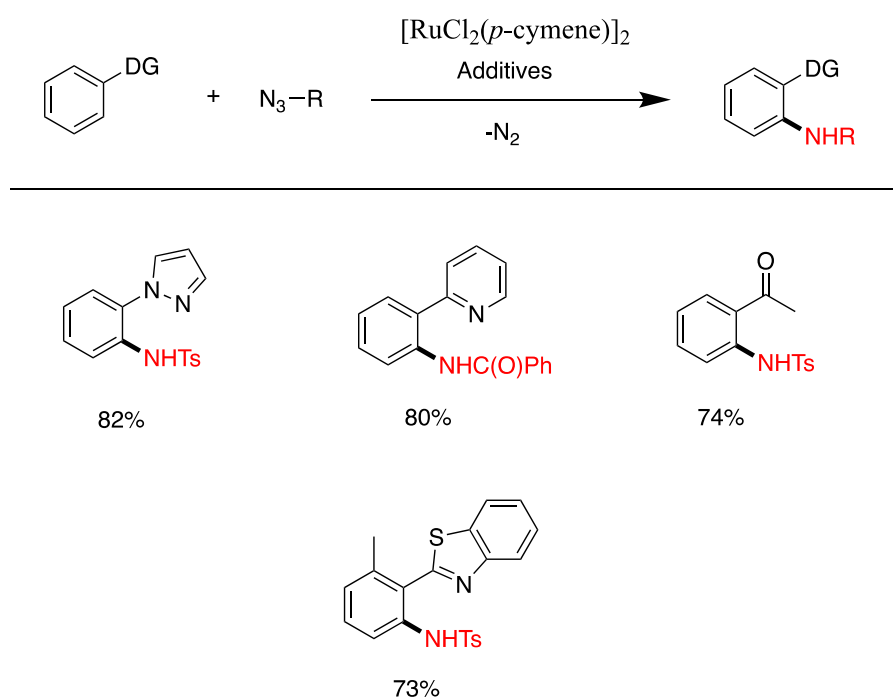
DFT calculations of free energies (kcal mol^{-1}) for the competing N-H and C-H activation



Scheme 4.15: Ru-catalysed para-selective and meta-C-H alkylation of aniline derivative; Bottom: DFT calculations of the most stable intermediates for the competing N-H and C-H activations with carbonate

base ($R = OH$) favouring *para*-functionalisation and with acetate base ($R = Me$) favouring *meta*-functionalisation.⁵⁸

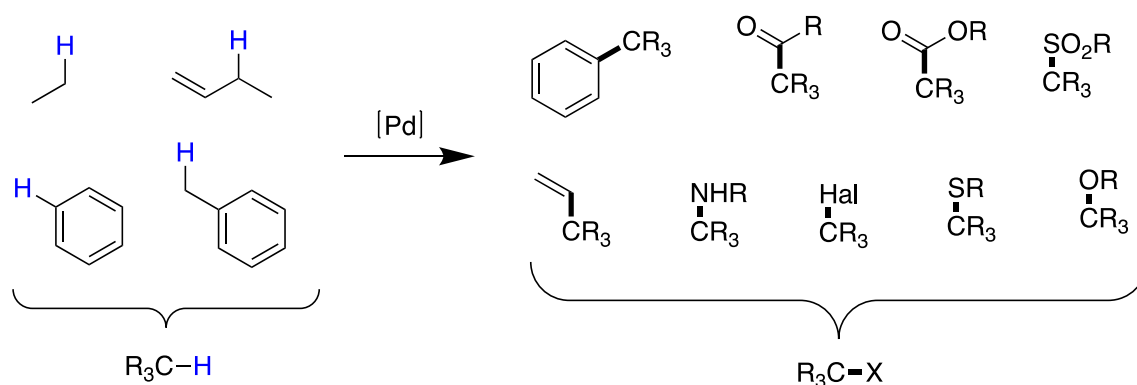
The use of Ru(II) catalysis has also been employed in C-H amination. For instance, several research groups including Chang, Ackermann, Ding and Sahoo have independently reported C-H amidation of heterocycles using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst with organic azides (Scheme 4.16).^{59–63}



Scheme 4.16: Ru(II) catalysed C-H amidation

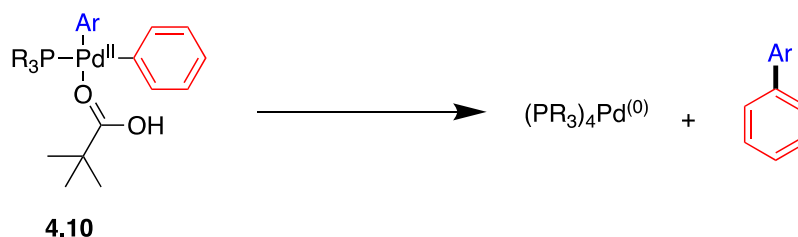
4.2.3 Palladium (Pd)

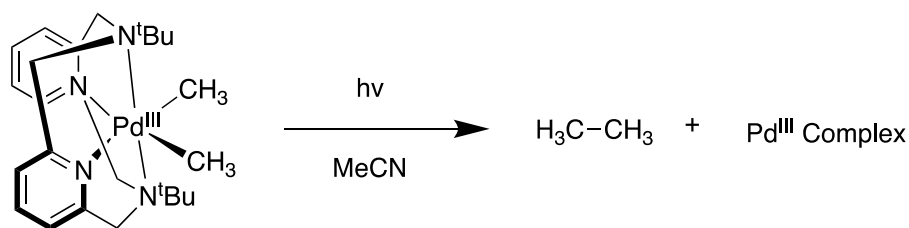
Pd-catalysed C-H activation methodologies are remarkably versatile in terms of the substrate and product scope and can be used for the synthesis of both simple and complex molecules. Pd catalysts are compatible with a variety of conditions and can be applied with a wide range of functional groups. These advantages make Pd catalysts possibly the most well-known and well-developed catalysts for C-H functionalisation in organic chemistry.^{64,65}



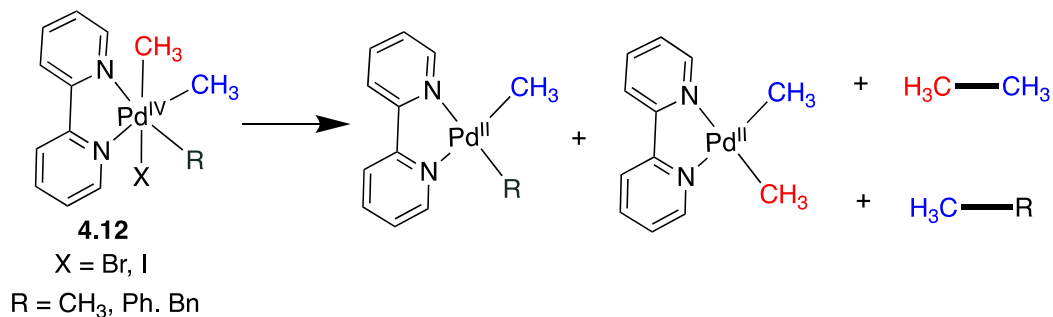
Scheme 4.17: Substrate and product scope in C-H functionalisation under Pd catalysis

A wide range of experimental and computational studies are available on the reactivity patterns of Pd complexes in C-H functionalisation.^{66–68} The catalytic C-H functionalisation reactions have used all four oxidation states Pd (0), Pd (I), Pd (II) and Pd (IV) and the catalytic cycles are commonly identified as Pd^{0/II} and Pd^{II/IV} pathways, determined by the oxidation states of the relevant intermediate complexes in respective catalytic cycles. Numerous organometallic palladacycles have been isolated and characterised for most of these oxidation states.^{68–70} Although most C-H activations under Pd catalysis are known to occur at Pd^{II} complexes, some C-H activations have also been found to be occurring at Pd^{IV} centres.^{71,72} Subsequent C-H functionalisation steps may occur from different oxidation states of Pd. For instance, C-C bonds may form through Pd^{II}, Pd^{III} or Pd^{IV} complexes, whereas, C-X bond formation protocols often employ strong oxidants and are known to occur through high-oxidation state Pd centres. Scheme 4.18 showcases some selected examples of palladacycles with different oxidation states in Pd-catalysed C-H activation.^{73–76}



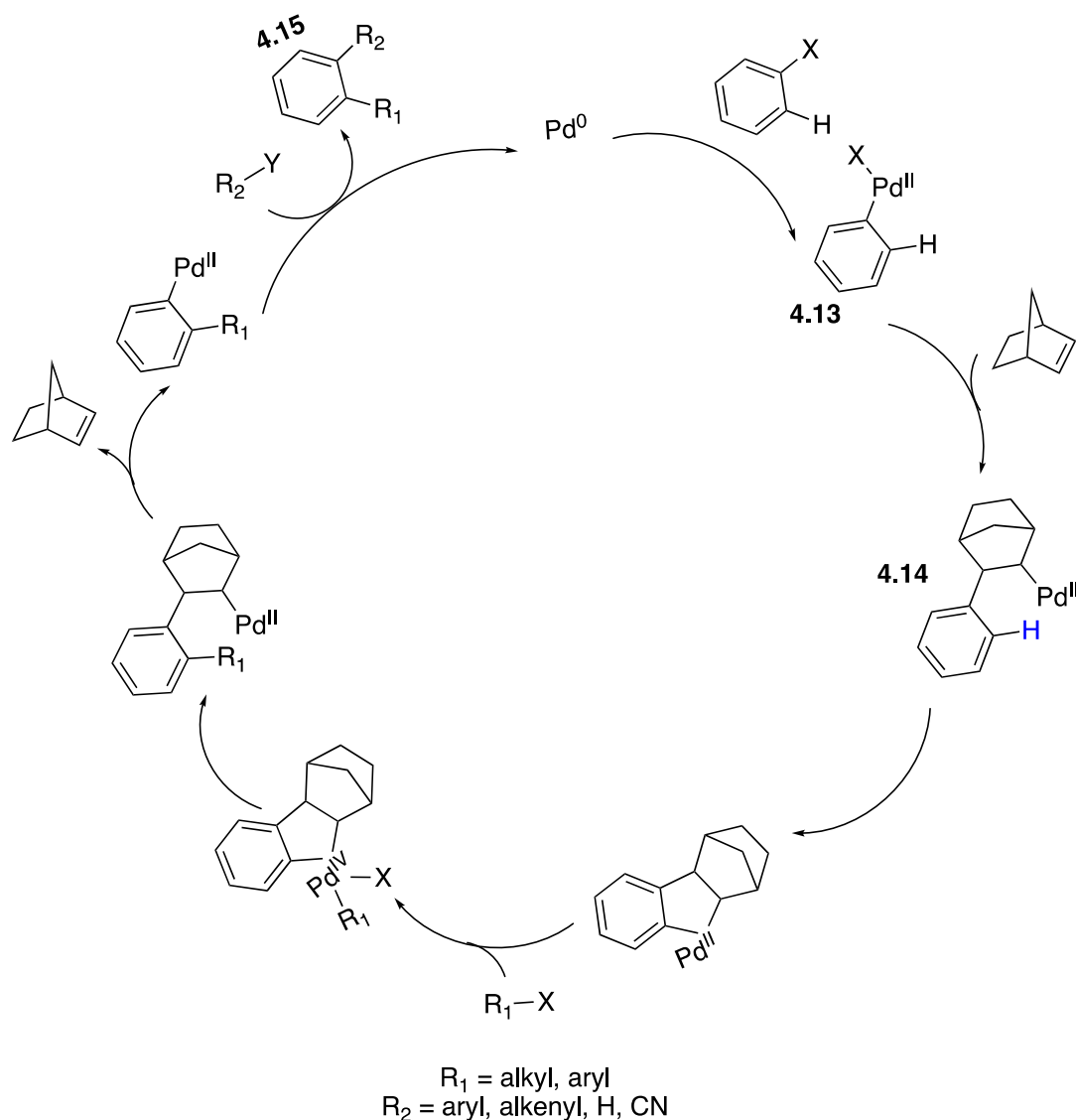


4.11



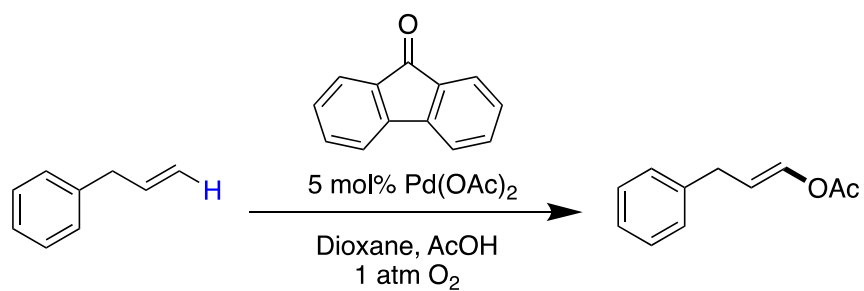
Scheme 4.18: Selected examples of palladacycles with different oxidation states in Pd-catalysed C-H activations.

Functionalising several positions on an aromatic system in one-pot is also possible through Pd catalysed C-H activation. Such Catellani-type reactions start with an oxidative insertion of the catalyst into a C-X bond as shown in Scheme 4.19, followed by the reaction of the resulting Pd (II) complex (**4.13**) with norbornene to afford the Pd-intermediate, **4.14**. The intermediate undergoes C-H activation in the ortho-position to the original insertion site. The catalyst is finally regenerated after the elimination of norbornene followed by the C-H activation of the new Pd-C_{Ar} bond which generates functionalised products such as **4.15**.^{77,78}

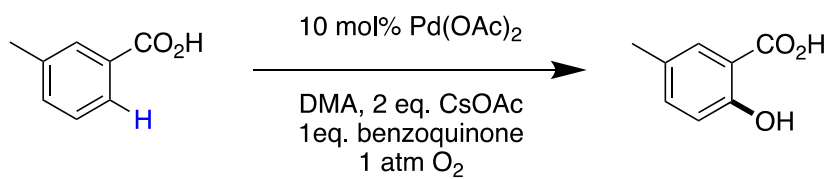


Scheme 4.19: One-pot C-H functionalisations at more than one position.

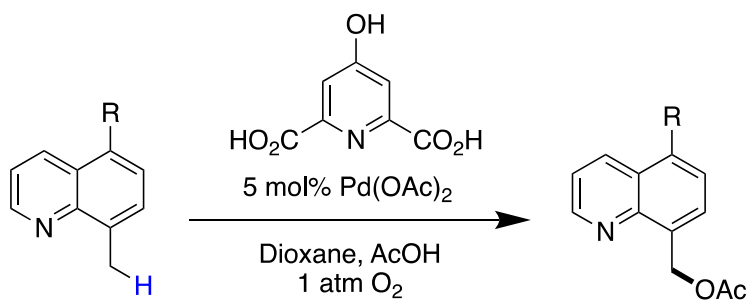
In oxidative C-H functionalisation, remarkably oxygen can be used as terminal oxidant under Pd catalysis. Many oxidative Heck reactions, *i.e.*, $C_{Ar}-H$ olefinations occur using O_2 as an oxidant. Numerous highly selective aerobic dehydrogenative aryl couplings have also been developed using such protocols.^{79–81} Furthermore, the use of O_2 as an oxidant is also applicable to other types of C-H functionalisation, such as C-H oxygenations. By varying the catalytic conditions in such reactions, formation of C-O bonds in allylic (Scheme 4.20), aromatic (Scheme 4.21), benzylic (Scheme 4.22) and aliphatic (Scheme 4.23) positions can be achieved with efficient atom economy.^{82–84}



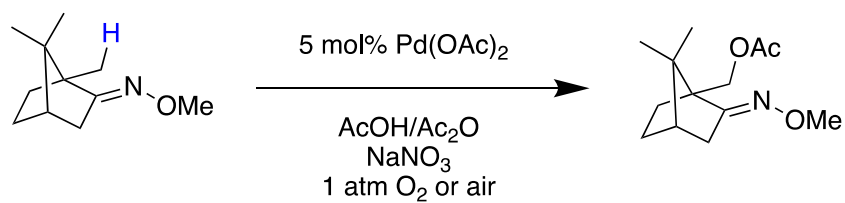
Scheme 4.20: C-H oxygenation in the allylic position



Scheme 4.21: C-H oxygenation in aromatic position

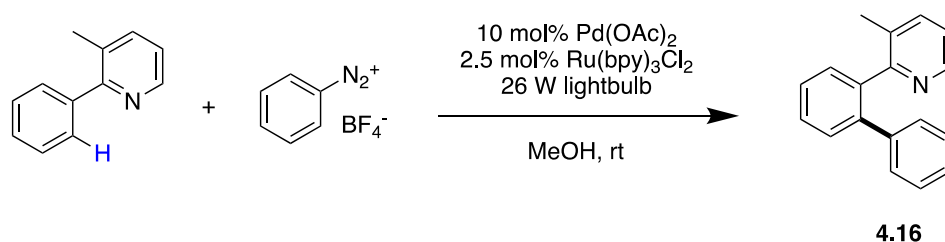


Scheme 4.22: C-H oxygenation in the benzylic position



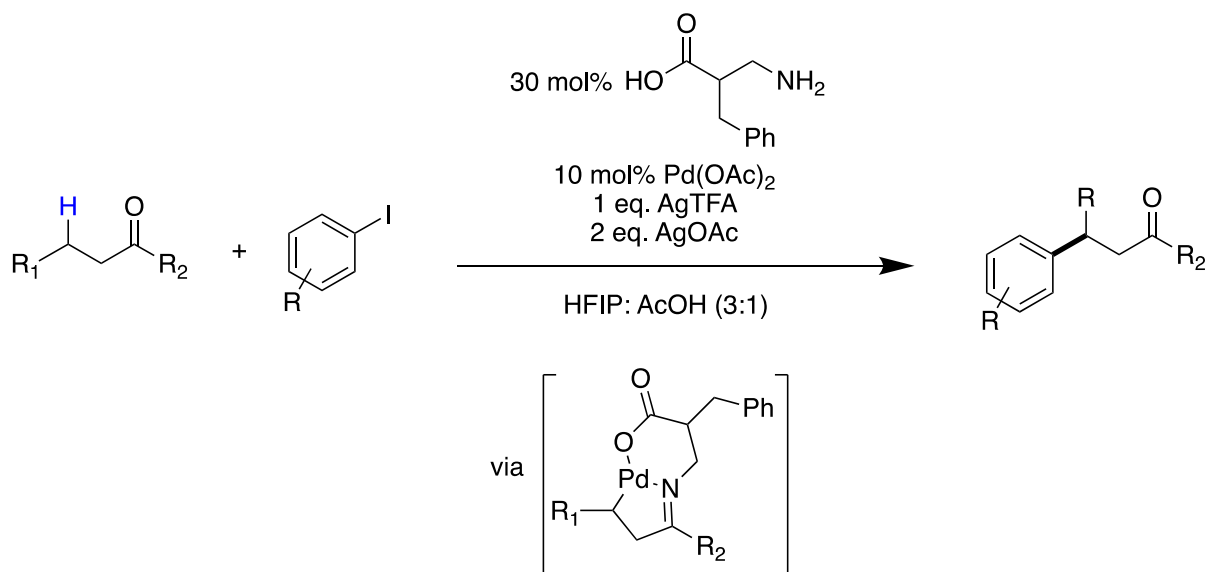
Scheme 4.23: C-H oxygenation at the aliphatic position

The use of oxidants in Pd catalysed C-H activation reactions is not limited to oxygen, there are several examples of two electron oxidants and one electron oxidant, including metal salts and organic oxidants. Some studies have focused on combining C-H activation chemistry with other types of chemistry in order to achieve the optimal results under milder reaction conditions and more atom-economy.⁸⁵ Scheme 4.24 represents one such protocol reported by Sanford *et al.*, in which the C-H functionalisation of the 2-phenylpyridine occurs at room temperature with visible light photocatalysis to afford the biaryl product **4.16**.⁸⁶



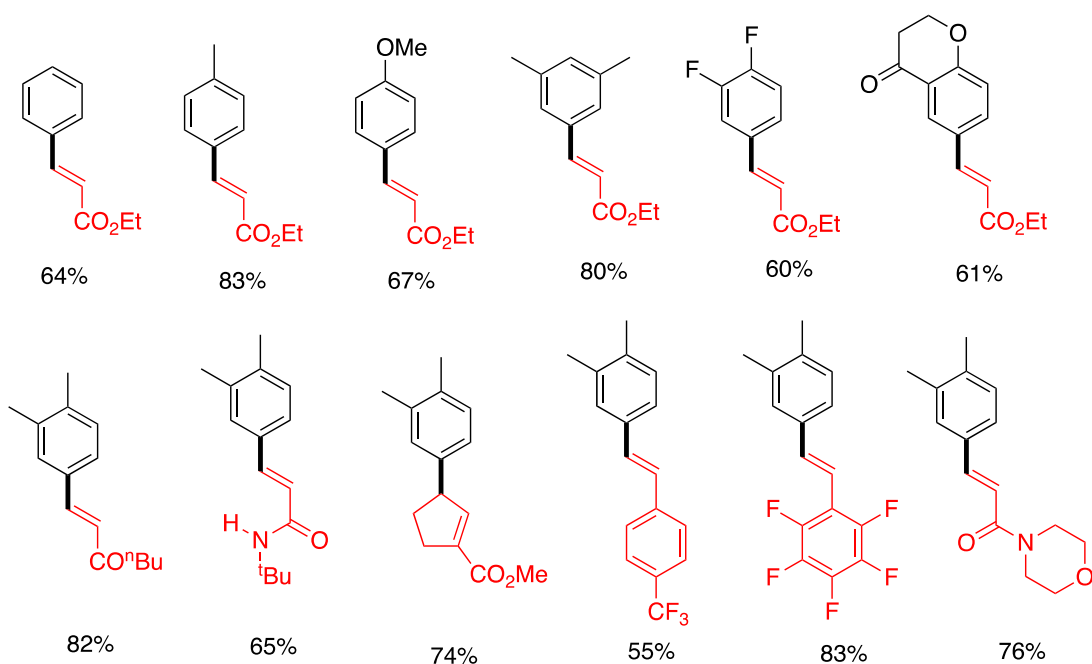
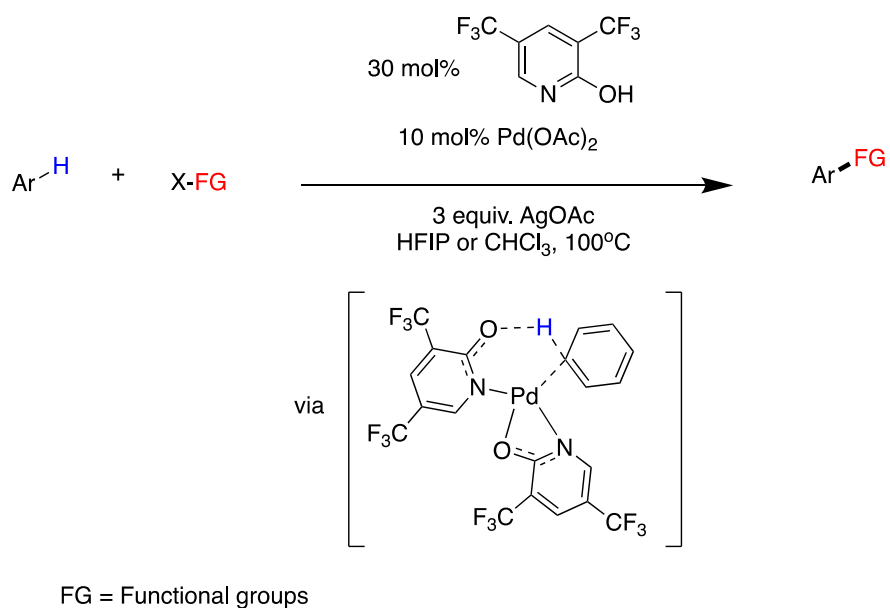
Scheme 4.24: Pd catalysed C-H arylation with visible light photocatalysis

Recently, there have been studies on the flexibility of the directing groups in Pd catalysed C-H bond functionalisations. A protocol developed by Yu and co-workers employs transient directing group to β -C(sp³)-H aliphatic ketones (Scheme 4.25). The formation of the six-membered Pd complex intermediate with α -benzyl β -alanine directing group was found to be crucial for the C-H bond activation.⁸⁷



Scheme 4.25: C-H arylation using a transient directing group

Another recent development by Yu and co-workers reports ligand-accelerated non-directed C-H functionalisation of arenes (Scheme 4.26). A Pd complex is formed with the 2-pyridone ligand that accelerates the reaction, which is compatible with a range of aromatic substrates. The methodology is also applicable to a variety of transformations including C-H olefination and C-H carboxylation reactions.



Scheme 4.26: Pd catalysed ligand – accelerated non-directed C-H functionalisation of arenes.

The combined effect of steric and electronic factors controls the site selectivity in these reactions. The pyridone ligand enhances the effect of sterics on the selectivity, thereby, provides further selectivity to non-directed C-H functionalisation.⁸⁸

The above discussion highlights a few selected metal catalysed C-H functionalisation protocols. Many other metal catalytic systems have been developed in this field including nickel-, iron-, copper- and cobalt- catalysed C-H activations. The use of C-H

functionalisation protocols has enabled the synthesis of many complex molecules with a greener approach. Late-stage C-H functionalisation protocol, in which libraries of complex bioactive molecules can be synthesised efficiently, has greatly contributed in speeding up the process in medicinal chemistry. Direct C-H functionalisations are continuing to advance and therefore should continue to greatly contribute to energy efficient, highly selective, atom-economic transformations for the synthesis of organic molecules and bioactive compounds in the future.^{89–97}

4.3 NUDT7 - a peroxisomal CoA diphosphatase

NUDT7 is a member of the superfamily of enzymes, Nudix hydrolases, which are found in all types of organisms and hydrolyse a wide range of pyrophosphates. In 1996, Bessman termed Nudix hydrolases as “housecleaners”, “cleansing the cell of potentially deleterious endogenous metabolites and modulating the accumulation of intermediates in biochemical pathways”.^{98,99} Nudix enzymes mainly act upon substrates of general structure **nucleoside diphosphate** linked to some moiety **X**. These include nucleoside di-, triphosphates, nucleoside sugars and alcohols, dinucleoside polyphosphates, dinucleotide coenzymes and RNA caps with varying degrees of substrate specificity.¹⁰⁰ Along with playing a vital role in removing potentially toxic nucleotide metabolites from the cell, these enzymes also regulate the availability and concentrations of various nucleotide substrates, cofactors and signalling molecules.

So far, 24 Nudix genes have been identified in mammals, many of which encode more than one isoform. Two isoforms of NUDT7 have been identified: NUDT7 α and NUDT7 β . The former is a peroxisomal CoA diphosphatase, whereas NUDT7 β is an inactive variant. NUDT7 α along with NUDT19 (another member of the Nudix family) are located in the peroxisome. Peroxisomes are ubiquitous organelles that are found in yeast, fungi, plants and animals, and regulate diverse metabolic functions.¹⁰¹ One typical function of peroxisome is the degradation of a wide range of carboxylic acids via α and β oxidation. This crucial process is suggested to be the driving force for the evolution of peroxisomes. A number of enzymes catalyse the β oxidation reactions. A variety of auxiliary enzymes are involved in the regulation of β oxidation, uptake of fatty acids and

cofactors required for β -oxidation. NUDT7 is one of these enzymes. The other auxiliary enzymes for β -oxidation include acyl-CoA thioesterases (ACOTs), membrane transporters/channels, acyl-CoA: amino acid N-acyltransferases and carnitine acyltransferases and some other members of the Nudix hydrolases.^{102,103}

CoA is involved in a vast number of reactions in intermediary metabolisms and is crucial in living organisms. NUDT7 α and NUDT19 (members of the Nudix hydrolases contained in the peroxisome) catalyses the degradation of CoA by hydrolysing free CoA and CoA esterified to various fatty acids to varying chain lengths of acyl-phosphopantetheines and 3',5'-ADP. The ACOTs, on the other hand, catalyse the hydrolysis of acyl-CoAs into the free fatty acid and CoA.^{104–107}

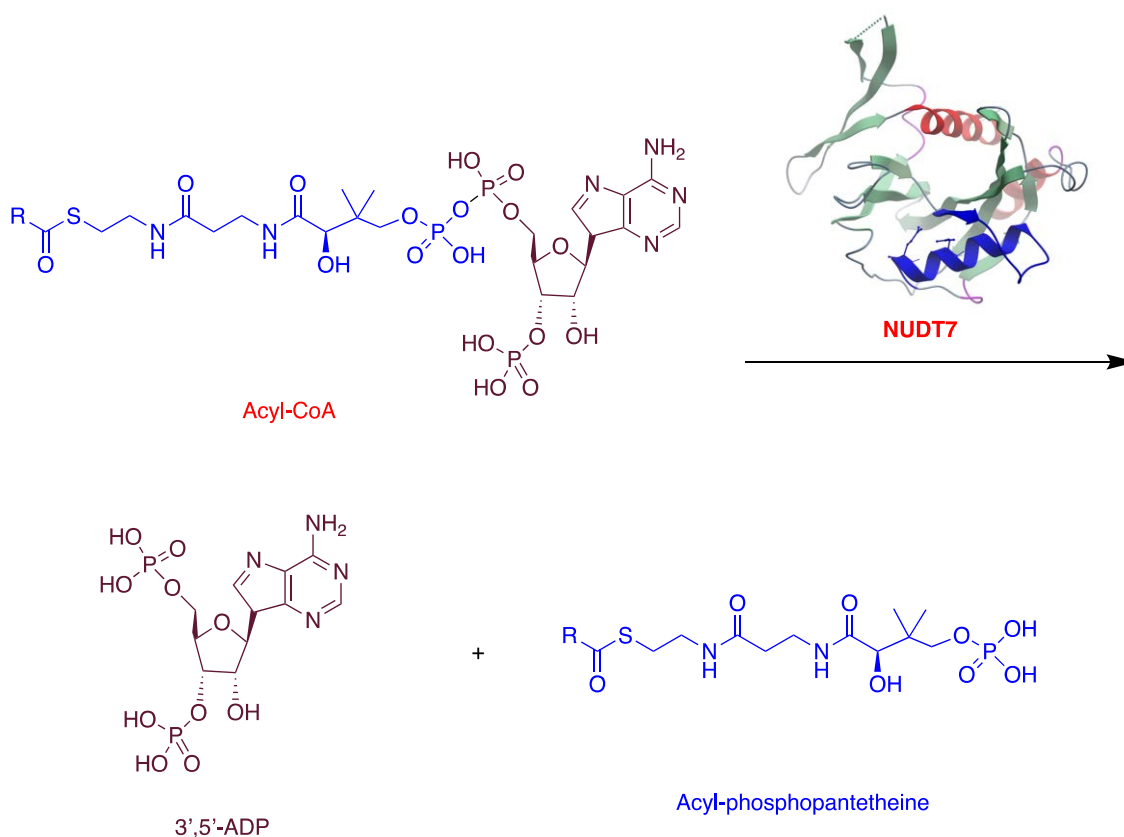


Figure 4.1: NUDT7 cleaves acyl-CoA into varying chain lengths of acyl-phosphopantetheines and 3',5'-ADP

The characterisation of the NUDT7 α function revealed that it cleaves acyl CoAs and CoAs and thereby serves two functions of regulating CoA levels and regulating β -

oxidation activity. NUDT7 α are expressed in the tissues with high expression of β -oxidation enzymes. NUDT7 α is highly expressed in the liver, adipose tissue, heart, mammary gland, stomach, lungs, kidney, brain and many others. By metabolising varying (typically medium to long) chain lengths of acyl-CoAs, NUDT7 α play key role in controlling β -oxidation activity in peroxisomes. Enzymes like NUDT7 have also been proposed to perform significant functions in clearing metabolites from the peroxisome.^{103,107}

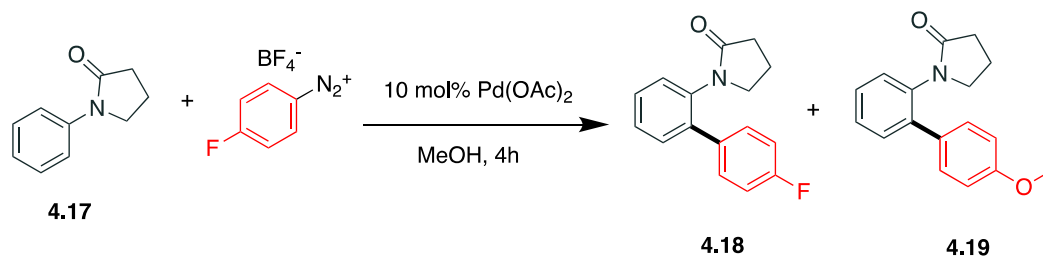
As stated above CoA is indispensable in living organisms, highly involved in intermediary metabolism reactions and if misregulated can lead to various diseases. Thus, NUDT7 α being one of the regulators of CoA level in the peroxisome, is also thought to be involved in numerous diseases. Recently, the upregulation of NUDT7 α has been associated with high risk of inflammatory bowel disease. Other diseases it has been implicated in include colorectal cancer and pantothenate kinase-associated neurodegeneration (PKAN).^{108,109}

Although, there have been many studies to investigate and understand the important functions of NUDT7 α , the molecular basis for its substrate recognition and the catalytic mechanism is still not fully understood. One of the aims of this chapter was to identify and synthesise a library of molecules that bind to the binding pocket of NUDT7 α , which, may help to understand its substrate recognition pattern and thereby, provide better insight into the catalytic mechanism and how it affects various diseases.

4.4 Results and Discussion

The Pd merged photocatalysis method, introduced in Chapter 3, combined with nuisance effect has been extended to other substrates known to undergo C-H activation and originally studied by the Sanford group.¹¹⁰ Hence, para-fluorobenzenediazonium tetrafluoroborate was reacted with 1-phenylpyrrolidin-2-one (Table 1) and different reactions parameters were studied.

Table 4.1: Optimising C-H activation conditions.



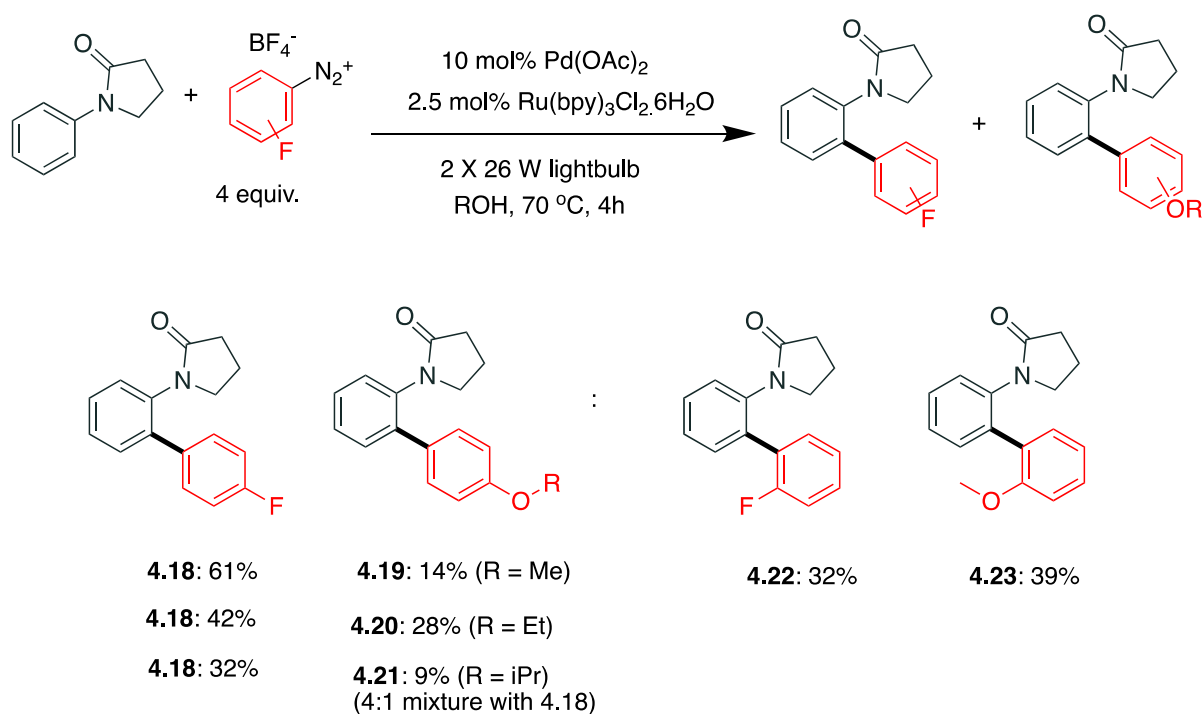
Entry	Light source	$\text{Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ mol%	Temp.	Conversion LC-MS (%) (4.18: 4.19)
1	a	2.5	reflux	85 (8:1)
2	daylight	2.5	reflux	60 (2:1)
3	b	2.5	reflux	25 (2:1)
4	a	-	reflux	65 (6:1)
5	a	-	r.t.	58 (20: 1)
6	b	-	reflux	20 (99: trace)

^a 26W compact fluorescent light bulb. ^b in absence of light.

The best condition (entry 1) gave excellent conversion (85%), which equates to a good 75% combined isolated yield of **4.18** and **4.19**. Entries 4 and 5 correspond closely to the earlier work of Sanford *et al.*, who obtained a 62% conversion to **4.18** in the absence of a Ru catalyst, at ambient temperature, whereas Entry 6 shows that low conversions are observed in the absence of light.

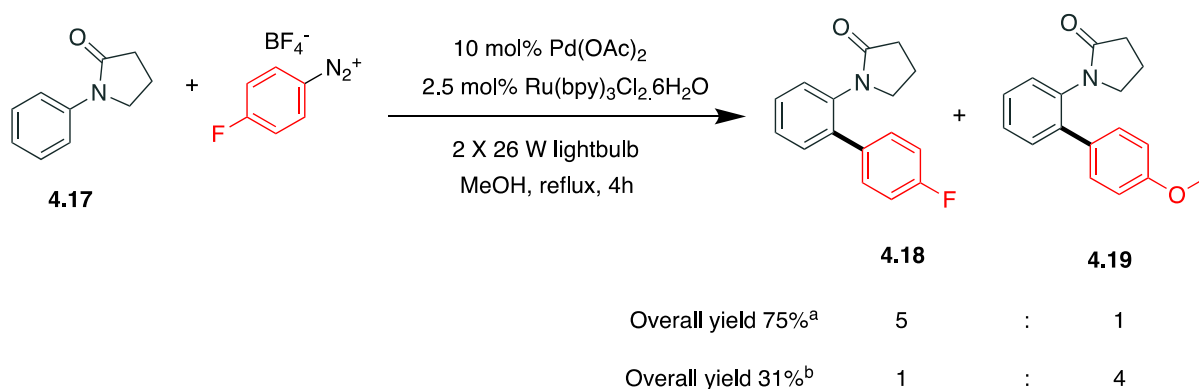
Using the optimized conditions, a small array of arylated products was formed, where we intended to form both the expected “Sanford arylation” products **4.18**, **4.22** along with the “nuisance product” **4.19** - **4.21**, **4.23** (Scheme 4.27). In this protocol, methanol and ethanol worked well as solvents and resulted in decent yields of the combined fluoroaryl and ether products, 75% and 70% respectively. Whereas 2-propanol did not work as well, possibly owing to the sterics affording a combined yield of 41% and t-butanol did not

lead to any product at all. Interestingly, a higher ratio of the ether product from ethanol was achieved in comparison with methanol, i.e. **4.19** vs. **4.20**.



Scheme 4.27: 1-phenylpyrrolidin-2-one derivatives (isolated yields)

It was anticipated that the ratio of the products can be influenced by the sequence in which the reactions were performed; for instance, the ratio of the methoxy-product **4.19** vs. product **4.18** was significantly increased when the diazonium salt was refluxed in methanol first, to favour the S_NAr process, and the substrate and catalysts were added later to the reaction, albeit with significantly lower overall yields, as shown in Scheme 4.28.

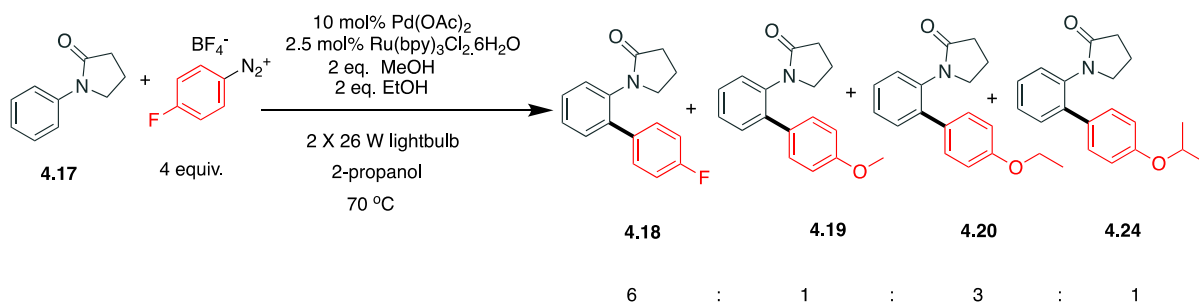


Scheme 4.28: Scope for controlling the ratio of products

^a One pot procedure (4h)

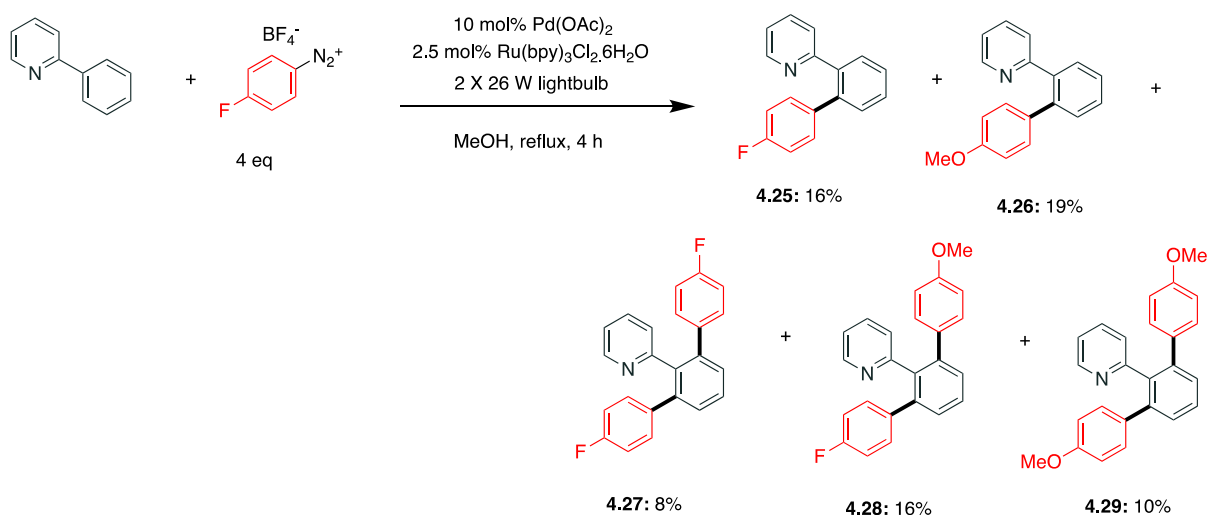
^b 4-fluorobenzenediazonium salt and MeOH were refluxed first (1h) then the other components were added and reacted for 4h.

Gratifyingly, a one-pot test reaction, employing separate alcohols led to a small array of ether products alongside the expected fluorobiphenyl **4.18** (Scheme 4.29). This made use of the relatively poor reactivity of isopropanol, which was used as the solvent and, given its large excess, was nevertheless able to react to a small extent. The ratio of the mixture was obtained by LC-MS and it was not purified further.



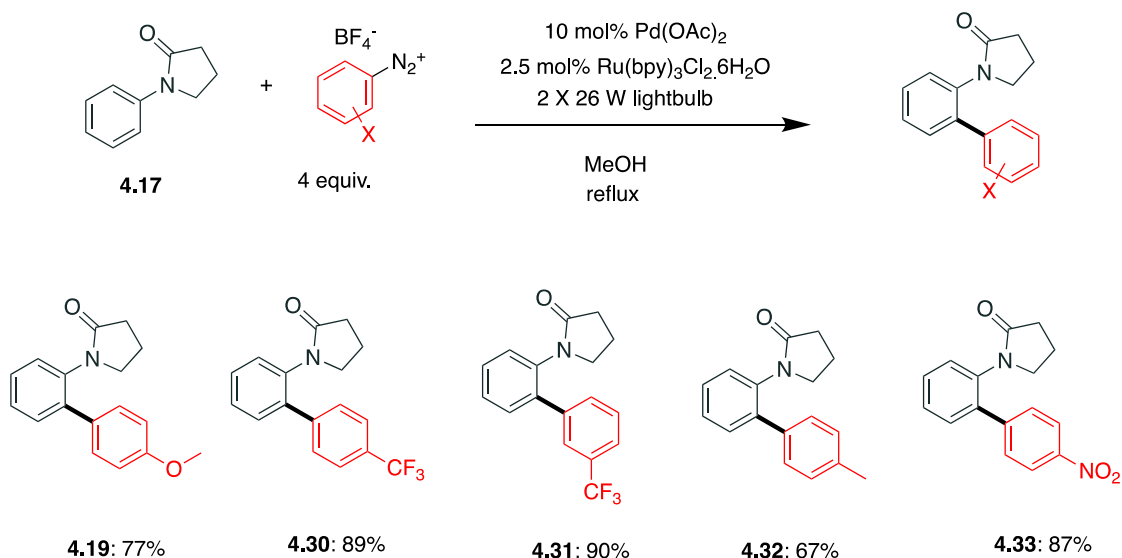
Scheme 4.29: Small array of 1-phenyl-2-pyrrolidinone derivatives formed from a mixture of alcohols

Finally, to test the limits of this chemistry, reaction of 2-phenylpyridine with the 4-fluorobenzenediazonium salt under reflux in methanol, led to five separable products, resulting from a combination of mono, di-arylation and “nuisance effects” (Scheme 4.30).



Scheme 4.30: A small array of 2-phenylpyridine derivatives from “nuisance effect” combined C-H arylation

We next wished to test the scope and limitations of the Sanford arylation on substrates incapable of undergoing the nuisance effect. Therefore, we synthesised a small array **4.30-4.33** as well as the known **4.19**.



Scheme 4.31: Ortho-arylated 1-phenyl-2-pyrrolidinone derivatives.

To test the usefulness of the Sanford arylation/nuisance effect protocol in medicinal chemistry, we looked at synthesising small arrays, either as mixtures or as separable fractions, based around privileged scaffolds (e.g. BZDs in Chapter 3, 2-phenylpyridines, 1-phenyl-2-pyrrolidinones) for biological assays. Subsequently, the arrays of the synthesised compounds were tested against different biological targets by our collaborators at the SGC. The initial biological screening revealed that compound **4.19** readily binds to NUDT7 α and the preliminary solved co-crystal x-ray structure is shown in Figure 4.2.

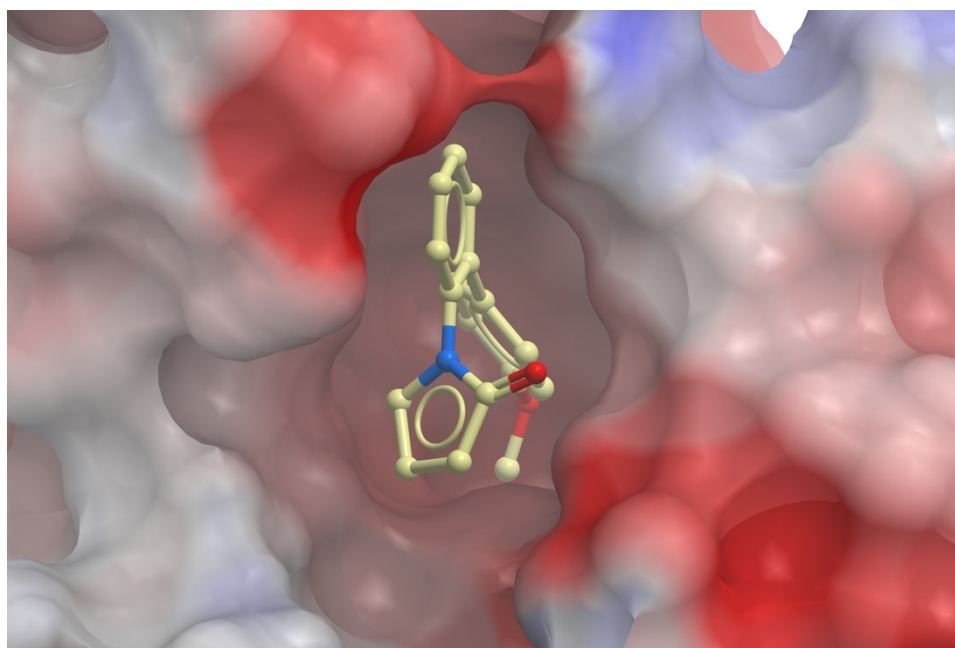


Figure 4.2: X-ray co-crystal of 4.19 bound to NUDT7 α

Figure 4.3 shows an overlay of independent X-ray co-crystal structures of two compounds, where a carbamate fragment **NU181** bound in close proximity of **4.19** in the binding pocket.

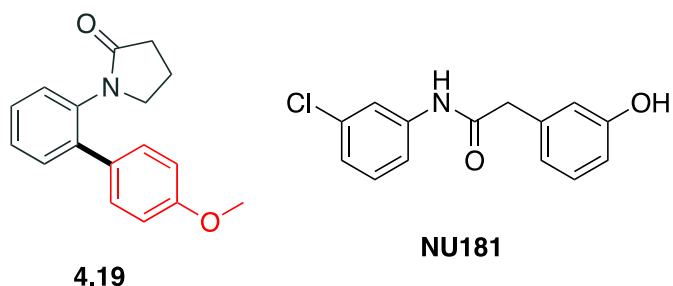
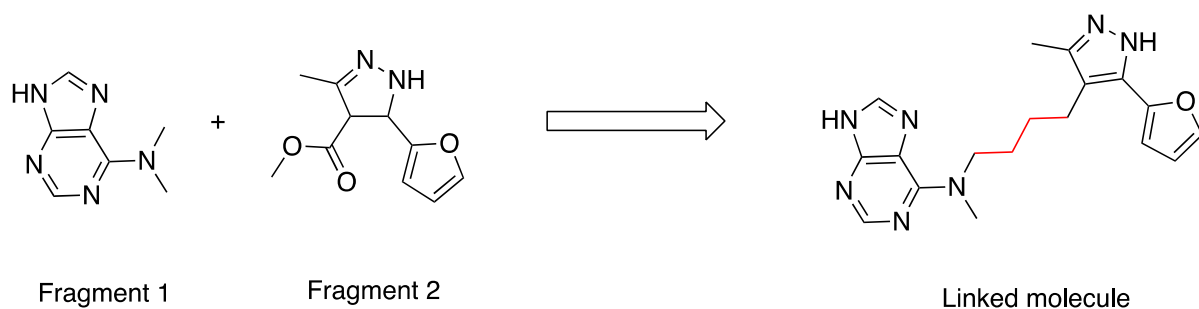


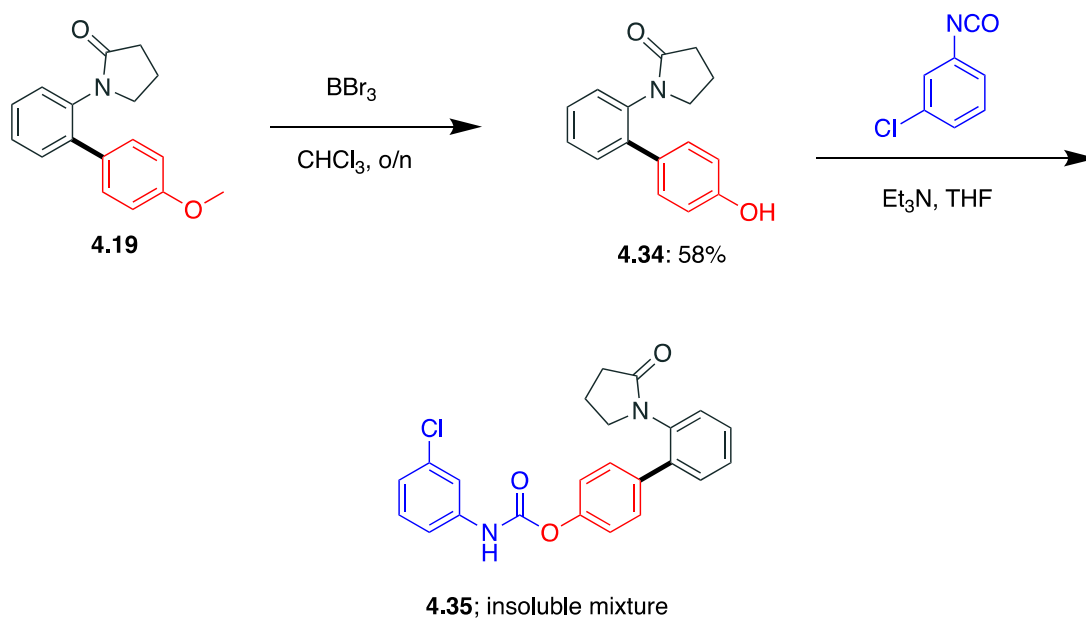
Figure 4.3: An overlay of **4.19** and **NU181** bound to NUDT7 α (top).

This provided a basis/guideline for a further series of fragment-linked phenylpyrrolidinones. There are many examples of “fragment-linking” in medicinal chemistry to achieve higher biological potency. The starting point of fragment linking can be determined by identifying the binding mode and key interactions of the fragments and the target protein. Typically, two non-overlapping molecules that bind to proximal sites are linked together to obtain a boost in potency.^{111–116} An exemplary case is the discovery of a novel Hsp90 (heat shock protein 90 – an anti-cancer target) inhibitor by fragment linking. Two fragment hits were joined to give the linked molecule in Scheme 4.32, where the successful fragment linking led to a 1000-fold increase in the binding efficiency. In the ternary structure fragment 1 and fragment 2 were about 3 Å apart from each other and computational modelling predicted that linking them with four atoms would provide the correct length.¹¹⁷



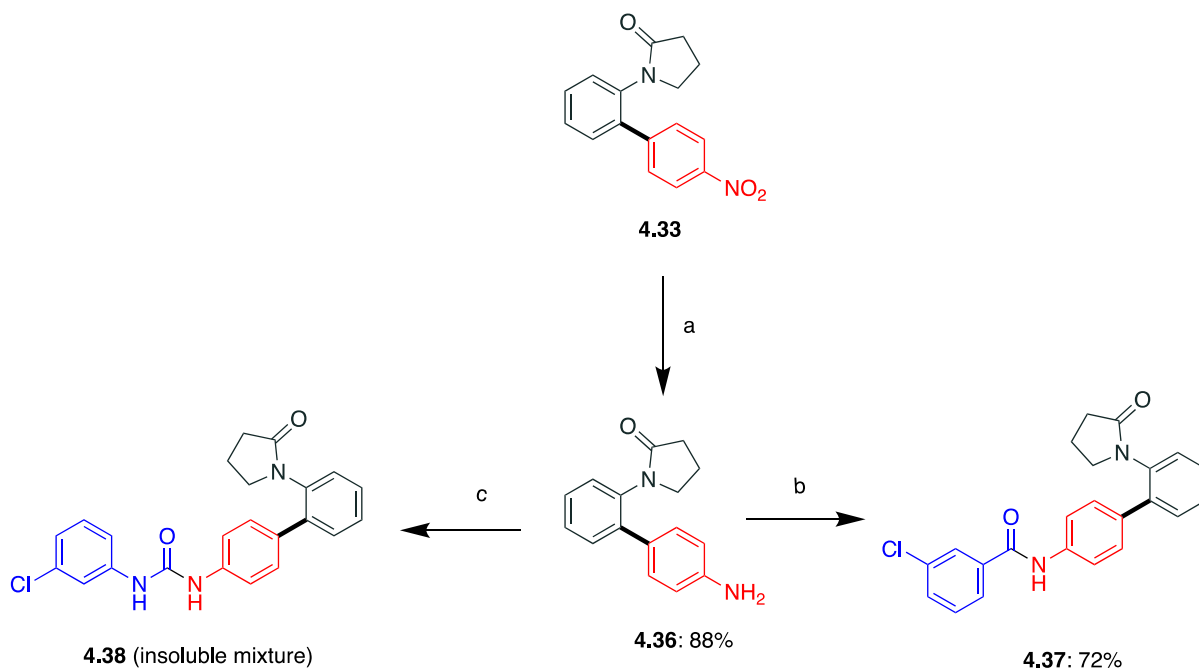
*Scheme 4.32: **Fragment 1**, $IC_{50} = 1500 \mu M$; **Fragment 2**, $IC_{50} = 1000 \mu M$; **Linked molecule** $IC_{50} = 1.5 \mu M$*

Our aim was to combine **4.19** and NU181 to synthesise compounds such as **4.35**, **4.38** and **4.39**. In the attempt to synthesise compound **4.35**, the following approach was taken, shown in Scheme 4.29. The dealkylation of **4.19** using boron tribromide resulted in **4.34**, which was further reacted with the isocyanate, however, the resulting compound was highly insoluble and could not be fully purified or characterised (Scheme 4.33).



*Scheme 4.33: Attempted synthesis of **4.35***

Next, the 4-nitrobiaryl pyrrolidinone compound **4.33** was reduced to **4.36** using tin (II) chloride dihydrate and the aminobiaryl product was further functionalised (Scheme 4.34). Compound **4.37** was prepared from **4.36** by direct acylation with the corresponding acyl chloride. However, analogous to **4.35**, compound **4.38** was highly insoluble and proved to be difficult to purify and characterise.



Scheme 4.34: Functionalisation of 1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one. a) SnCl₂·2H₂O, EtOAc, 70°C, o/n; b) 3-chlorobenzoyl chloride, Et₃N, CH₂Cl₂, o/n; c) 3-chlorophenyl isocyanate, Et₃N, CH₂Cl₂, o/n.

Next, we aimed to synthesise covalent modifying compounds to target cysteine residues, since the trifluoromethylbiaryl compound, **4.31** shows interactions with a proximal cysteine residue (Figure 4.5 - E).

Cysteines are good targets for non-covalent interactions such as halogen bonding, however, the most powerful approach for targeting cysteines is through covalent modifiers or 'irreversible' inhibitors. Covalent inhibitors are regarded as powerful tool for targeting cysteines as they require lower doses, have increased biochemical efficiency and longer duration of action, however, they also tend to lead to off-target toxicity due to the lack of selectivity.^{118–122} Typically, covalent inhibitors contain a highly reactive

electrophilic species, such as an α,β unsaturated ketones.¹²³ Figure 4.4 shows the generic structures of typical key units for covalent modifiers.

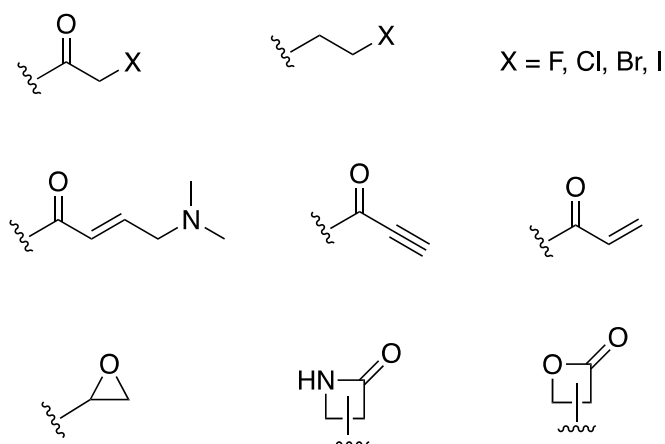
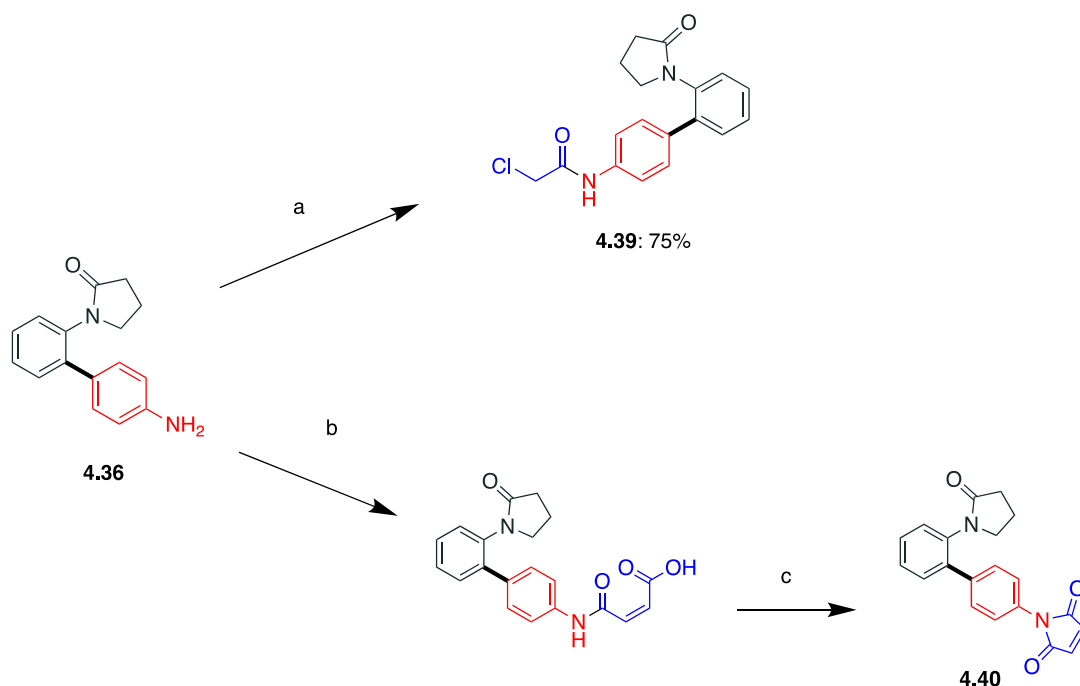


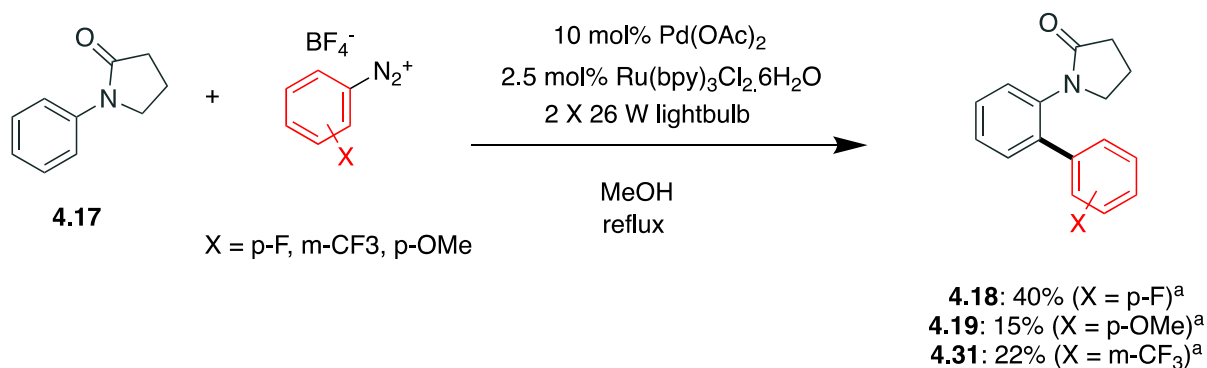
Figure 4.4: Structures of typical covalent modification key units

Compound **4.39** and **4.40** were designed with the aim to target proximal cysteine residues. Compound **4.39** was easily prepared from **4.36** by direct acylation with the corresponding acyl chloride. Compound **4.40** was synthesised via a two-step route. **4.36** was reacted with maleic anhydride in chloroform to produce the maleic acid derivative. The ring-closing occurs through dehydration to form the maleimide, **4.40**. (Scheme 4.35).



Scheme 4.35: a) chloroacetyl chloride, Et₃N, CH₂Cl₂, o/n; b) maleic anhydride, CHCl₃, 2h; c) Acetic anhydride, sodium acetate, 2h, reflux

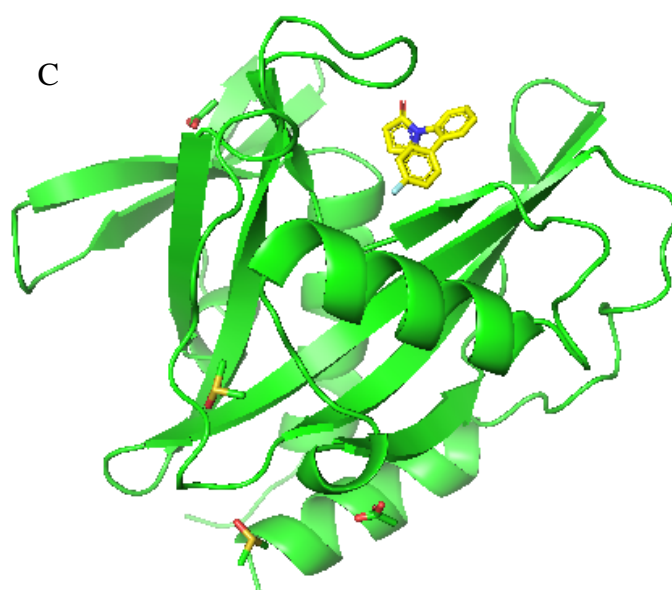
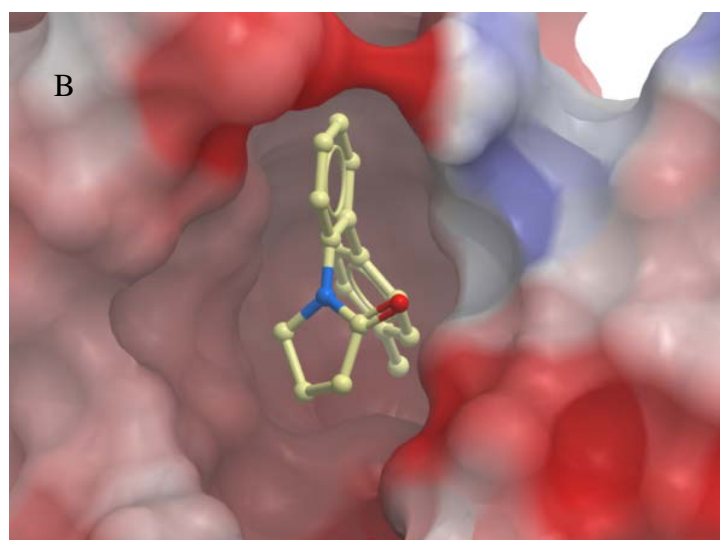
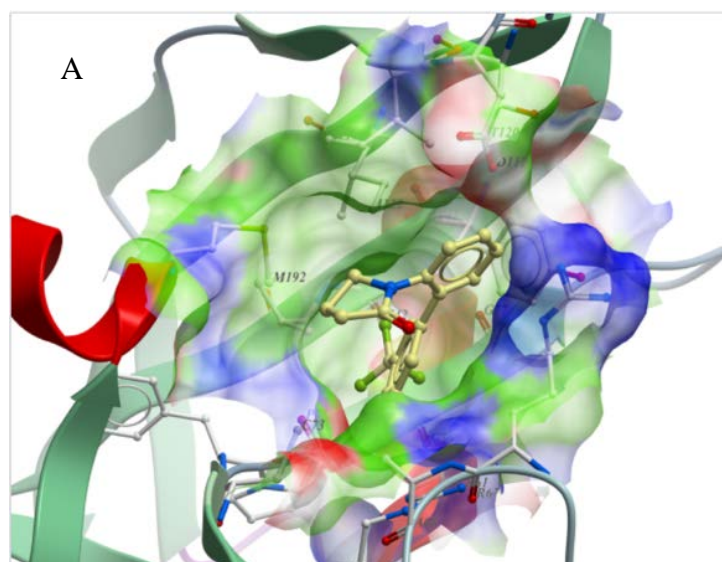
Finally, we wished to compare the effectiveness of the arylation chemistry carried out in a one-pot procedure versus the “single shot” protocol described above in Scheme 4.31. Hence, a mixture of ortho-arylated 1-phenyl-2-pyrrolidinone derivatives was synthesised employing different substituted diazonium salts in one-pot reaction (Scheme 4.36). The mixture was then subjected to X-ray crystallographic analysis as an array versus the individual components.



^a LC-MS conversion rates

Scheme 4.36: One-pot C-H arylation of 1-phenyl-2-pyrrolidinone employing several diazonium salts

All the compounds were biologically evaluated against NUDT7 α . A number of the compounds that bound to the protein were co-crystallised (Figure 4.5). In total, there were four compounds from the ortho-arylated 1-phenyl-2-pyrrolidinone derivatives that bound to NUDT7 α , however, none of the further functionalised derivatives, such as **4.38**, **4.39** or **4.40**, produced any hits. Only the para-fluorobiphenyl **4.18** was detected while conducting an X-ray crystallography of the mixture from Scheme 4.36.



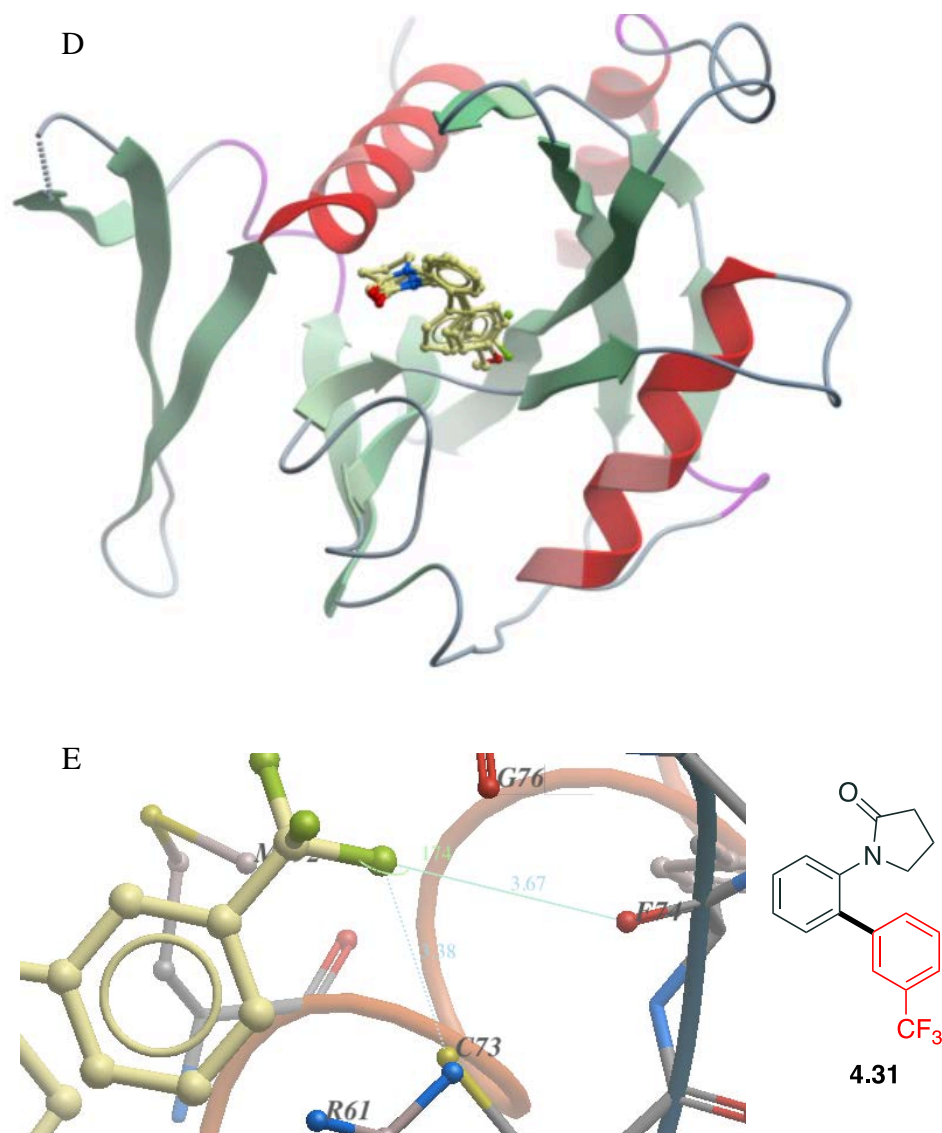


Figure 4.5: A) X-ray co-crystal structure of **4.31** With NUDT7 α ; B) co-crystal structure of **4.32** With NUDT7 α ; C) co-crystal structure of **4.18** with NUDT7 α ; D) Overlay of **4.19**, **4.31** and **4.32** in the binding pocket of NUDT7 α ; E) Interactions of **4.31** and cysteine residue of NUDT7 α : F to S distance is 3.38 Å and F to O is 3.67 Å.

4.5 Conclusions

Small arrays of 1-phenyl-2-pyrrolidone and 2-phenylpyridine derivatives were synthesised using Pd and photocatalysis merged with a “nuisance effect” C-H arylation method. The use of reflux temperatures and more reactive solvents (methanol or ethanol) in this protocol can lead to the production of a more diverse array of products.

The small arrays of compounds synthesised from single reactions using the “nuisance effect” were utilised for preliminary biological X-ray co-crystallisation studies. A number of derivatives of the 1-phenyl-2-pyrrolidone series showed successful binding to NUDT7 α (Figure 4.6). Further biological assays are currently being conducted by our collaborators to obtain preliminary binding data, which should help to build a more conclusive understanding about IC₅₀ values, the binding efficiency, binding patterns and SAR of these compounds.

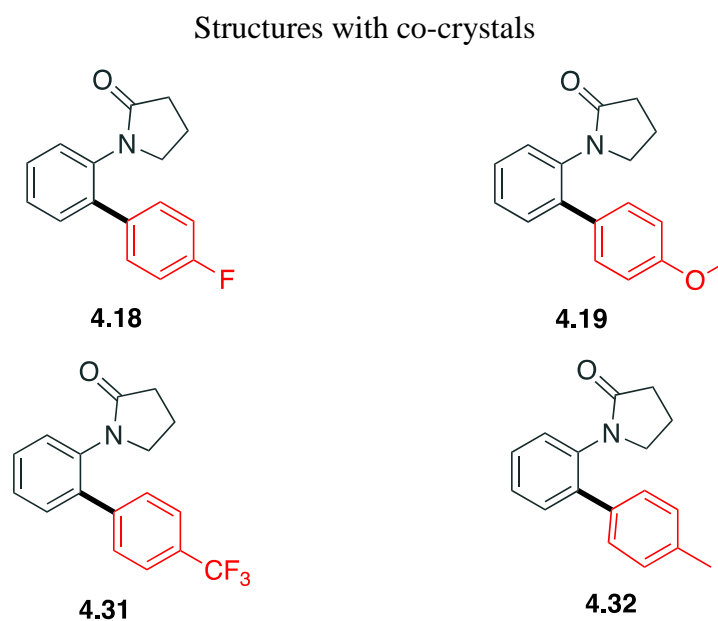


Figure 4.6: Structure of compounds co-crystallised with NUDT7 α

4.6 Experimental details for Chapter 4

See Chapter 2.4 for general experimental.

4.6.1 1-(4'-Fluorobiphenyl-2-yl)pyrrolidin-2-one (**4.18**); 1-(4'-Methoxybiphenyl-2-yl)pyrrolidin-2-one (**4.19**)

1-Phenyl-2-pyrrolidinone (0.065 g, 0.40 mmol), 4-fluorobenzenediazonium tetrafluoroborate (0.35 g, 1.67 mmol), palladium (II) acetate (0.009 g, 0.04 mmol) and Ru(bpy)₃Cl₂·6H₂O (0.007 g, 0.01 mmol) were suspended in degassed, anhydrous methanol (4 mL). Two fluorescent light bulbs (26 W) were placed on either side of the reaction vessel and the reaction mixture was heated at reflux for 4 hours under inert atmosphere. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (50 mL) and washed with water (20 mL) and aqueous sodium sulphite (10%, 35 mL x 2). The combined aqueous layers were extracted with ethyl acetate (50 mL) and thereafter the combined organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting crude material was purified by reversed phase chromatography (water/acetonitrile with 0.1% formic acid, 5 min at 0%, 30%-90%). The reaction generated two products, product **4.18** was obtained as a viscous oil (0.062 g, 61%) and Product **4.19** was obtained also as a viscous oil (0.015 g, 14%).

4.18: ¹H-NMR (500 MHz) CDCl₃: δ = 7.45 – 7.40 (m, ArH, 1H), 7.40 – 7.35 (m, ArH, 3H), 7.35 – 7.31 (m, ArH, 1H), 7.10 (pt, ³J_{HH} = 8.7 Hz, ArH, 2H), 3.25 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.43 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.92 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). The spectral data were concurrent with those reported.

4.19: ¹H-NMR (500 MHz) CDCl₃: δ = 7.39 – 7.36 (m, ArH, 3H), 7.33 – 7.29 (m, ArH, 3H), 6.97 – 6.92 (m, ArH, 2H), 3.85 (s, O-CH₃, 3H), 3.23 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.44 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.90 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). The spectral data were concurrent with those reported.⁸⁶

4.19 was synthesised on a larger scale by combining 1-Phenyl-2-pyrrolidinone (0.50 g, 3.1 mmol), 4-methoxybenzenediazonium tetrafluoroborate (2.75 g, 12.4 mmol), palladium (II) acetate (0.069 g, 0.31 mmol) and Ru(bpy)₃Cl₂·6H₂O (0.58 g, 0.078 mmol) were suspended in degassed, anhydrous methanol (30 mL). Two fluorescent light bulbs (26 W) were placed on either side of the reaction vessel and the reaction mixture was heated at reflux for 4 hours under inert atmosphere. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (50 mL) and washed with water (20 mL) and aqueous sodium sulphite (10%, 35 mL x 2). The combined aqueous layers were extracted with ethyl acetate (50 mL) and thereafter the combined organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting crude material was purified by reversed phase chromatography (water/acetonitrile with 0.1% formic acid, 5 min at 0%, 30%-90%). Product **4.19** was obtained as a viscous oil (0.64 g, 77%).

4.6.2 1-(4'-Ethoxybiphenyl-2-yl)pyrrolidin-2-one (**4.20**)

The same method as that of **4.18/4.19** was used but ethanol (5 mL) was used as the solvent instead of methanol. Starting material, 1-phenyl-2-pyrrolidinone (0.007 g, 0.043 mmol) was recovered and two products were generated, product **4.18** was obtained as an oil (0.038 g, 42%) and product **4.20** was obtained also as an oil (0.028 g, 28%).

¹H-NMR (500 MHz) CDCl₃: δ = 7.40 – 7.34 (m, ArH, 3H), 7.33 – 7.28 (m, ArH, 3H), 6.93 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 4.08 (q, ³J_{HH} = 7.0 Hz, O-CH₂CH₃, 2H), 3.23 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.44 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.89 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H), 1.45 (t, ³J_{HH} = 7.0 Hz, O-CH₂CH₃, 3H).

¹³C-NMR (126 MHz) CDCl₃: δ = 175.6 (C=O), 158.6 (ArC), 139.4 (ArC), 136.4 (ArC), 131.4 (ArC), 130.9 (ArC), 129.5 (2 x ArC), 128.4 (ArC), 128.1 (ArC), 127.9 (ArC), 114.4 (2x ArC), 63.5 (O-CH₂CH₃), 50.1 (COCH₂CH₂CH₂N), 31.2 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N), 14.8 (O-CH₂CH₃).

HRMS-ESI (m/z) calculated for C₁₈H₁₉NO₂ [+H]⁺: 282.1489, found: 282.1487. LCMS purity (UV) = 97 %, tR 11.85 min.

4.6.3 1-(4'-Propoxybiphenyl-2-yl)pyrrolidin-2-one (**4.21**)

The same method as that of **4.18/4.19** was used but 2-propanol (5 mL) was used as the solvent instead of methanol. Starting material, 1-phenyl-2-pyrrolidinone (0.027 g, 0.17 mmol) was recovered and two products were generated, product **7c** was obtained as a white solid (0.019 g, 32%) and a mixture of **4.18** and **4.21** was obtained an oil (0.0059 g, 9%) in 1:4 ratio as determined by $^1\text{H-NMR}$ and LC-MS.

4.18 & 4.21: $^1\text{H-NMR}$ (500 MHz) CDCl_3 : δ = 7.62 – 7.52 (m, ArH, 1H), 7.42 – 7.35 (m, ArH, 4H), 7.32 – 7.26 (m, ArH, 3H), 6.91 (d, $^3J_{\text{HH}}$ = 8.5 Hz, ArH, 2H), 4.62 – 4.55 (m, O-CHCH₃CH₃, 1H), 3.92 (t, $^3J_{\text{HH}}$ = 7.0 Hz, COCH₂CH₂CH₂N, 1H), 3.22 (t, $^3J_{\text{HH}}$ = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.64 (t, $^3J_{\text{HH}}$ = 8.0 Hz, COCH₂CH₂CH₂N 1H), 2.44 (t, $^3J_{\text{HH}}$ = 8.0 Hz, COCH₂CH₂CH₂N x 4, 8H; **7c**), 2.23 – 2.16 (m, COCH₂CH₂CH₂N, 1H), 1.90 (q, $^3J_{\text{HH}}$ = 7.5 Hz, COCH₂CH₂CH₂N, 2H), 1.37 (d, $^3J_{\text{HH}}$ = 6.0 Hz, O-CHCH₃CH₃, 6H).

HRMS-ESI (m/z) calculated for C₁₉H₂₁NO₂ [$+\text{H}$]⁺: 296.1650, found: 296.1647. LCMS ratio (UV) = **6a** 18%, tR 12.37 min, **7c**, 75%, tR 12.29 min.

4.6.4 1-(2'-Fluorobiphenyl-2-yl)pyrrolidin-2-one (**4.22**); 1-(2'-Methoxybiphenyl-2-yl)pyrrolidin-2-one (**4.23**)

This reaction was synthesised on a 0.30 mmol scale by the same procedure as **4.18/4.19** and 2-fluorobenzenediazonium tetrafluoroborate (0.25 g, 1.20 mmol). Starting material, 1-Phenyl-2-pyrrolidinone was recovered (0.006 g, 0.037 mmol) and two products were generated, product **4.22** was obtained as a viscous oil (0.022 g, 32%) and Product **4.23** was obtained as a viscous oil (0.027 g, 39%).

4.22: $^1\text{H-NMR}$ (500 MHz) CDCl_3 : δ = 7.46 – 7.42 (m, ArH, 1H), 7.41 – 7.37 (m, ArH, 2H), 7.36 – 7.31 (m, ArH, 3H), 7.20 – 7.16 (m, ArH, 1H), 7.15 – 7.10 (m, ArH, 1H), 3.39 (t, $^3J_{\text{HH}}$ = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.35 (t, $^3J_{\text{HH}}$ = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.91 (p, $^3J_{\text{HH}}$ = 7.5 Hz, COCH₂CH₂CH₂N, 2H).

$^{13}\text{C-NMR}$ (126 MHz) CDCl_3 : δ = 174.8 (C=O), 165.4 (d, $^1J_{\text{FC}}$ = 246.5 Hz, ArC), 137.8 (ArC), 133.5 (ArC), 131.6 (ArC), 131.5 (ArC), 131.4 (ArC), 129.6 (d, $^3J_{\text{FC}}$ = 8.0 Hz, ArC), 129.1 (ArC), 127.6 (d, $^3J_{\text{FC}}$ = 8.5 Hz, ArC), 126.7 (d, $^2J_{\text{FC}}$ = 16.0 Hz, ArC), 124.1

(d, $^4J_{\text{FC}} = 3.5$ Hz, ArC), 115.4 (d, $^2J_{\text{FC}} = 22.5$ Hz, ArC), 50.2 (COCH₂CH₂CH₂N), 31.3 (COCH₂CH₂CH₂N), 19.08 (COCH₂CH₂CH₂N).

HRMS-ESI (m/z) calculated for C₁₆H₁₄FNO [+Na]⁺: 278.0952, found: 278.0952. LCMS purity (UV) = 96 %, tR 12.30 min.

4.23: ¹H-NMR (500 MHz) CDCl₃: δ = 7.42 – 7.37 (m, ArH, 1H), 7.37 – 7.31 (m, ArH, 4H), 7.22 (d, $^3J_{\text{HH}} = 7.5$ Hz, ArH, 1H), 7.00 (d, $^3J_{\text{HH}} = 7.5$ Hz, ArH, 1H), 6.98 – 6.94 (m, ArH, 1H), 3.76 (s, O-CH₃, 3H), 3.26 (t, $^3J_{\text{HH}} = 7.0$ Hz, COCH₂CH₂CH₂CN, 2H), 2.34 (t, $^3J_{\text{HH}} = 8.0$ Hz, COCH₂CH₂CH₂N, 2H), 1.82 (p, $^3J_{\text{HH}} = 7.5$ Hz, COCH₂CH₂CH₂CN, 2H).

¹³C-NMR (126 MHz) CDCl₃: δ = 174.7 (C=O), 156.4 (ArC), 137.3 (ArC), 136.0 (ArC), 131.8 (ArC), 130.9 (ArC), 129.1 (ArC), 128.3 (ArC), 128.0 (ArC), 127.8 (ArC), 127.2 (ArC), 120.6 (ArC), 110.7 (ArC), 55.5 (O-CH₃), 49.9 (COCH₂CH₂CH₂N), 31.3 (COCH₂CH₂CH₂N), 19.2 (COCH₂CH₂CH₂N).

HRMS-ESI (m/z) calculated for C₁₇H₁₇NO₂ [+Na]⁺: 290.1151, found: 290.1151. LCMS purity (UV) = 94 %, tR 11.65 min.

4.6.5 Reaction with 2-Phenylpyridine

2-Phenylpyridine (0.078 g, 0.50 mmol), 4-fluorodiazonium tetrafluoroborate (0.42 g, 2.0 mmol), palladium (II) acetate (0.011 g, 0.05 mmol) and Ru(bpy)₃Cl₂·6H₂O (0.009 g, 0.013 mmol) were suspended in degassed, anhydrous methanol (4 mL). Two fluorescent light bulbs (26 W) were placed on either side of the reaction vessel and the mixture was heated at reflux for 4 hours. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (40 mL) and washed with water (20 mL) and aqueous sodium sulphite (10%, 35 mL x 2). The combined aqueous layer was extracted with ethyl acetate (50 mL) and thereafter the combined organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting crude material was purified by reversed phase chromatography (water/acetonitrile with 0.1% formic acid, 5 min at 0%, 30%-90%). Starting material, 1-phenyl-2-pyrrolidinone was recovered (0.008 g, 0.052 mmol) and five products were generated from this reaction:

2-(4'-Methoxybiphenyl-2-yl)pyridine (**4.25**)

Product **4.25** was obtained as a green/yellow oil (0.022 g, 19%). The spectral data were concurrent with those reported.⁵

2-(4'-Fluorobiphenyl-2-yl)pyridine (**4.26**)

Product **4.26** was obtained as a viscous oil (0.018 g, 16%). The spectral data were concurrent with those reported.⁵

2-(4,4'-Methoxybiphenyl-2,6-yl)pyridine (**4.27**)

Product **9c** was obtained as a green/yellow oil (0.016 g, 10%). The spectral data were concurrent with those reported.⁵

2-(4,4'-Fluoromethoxybiphenyl-2,6-yl)pyridine (**4.28**)

Product **4.28** was obtained as a viscous oil (0.024 g, 15%).

¹H-NMR (500 MHz) CDCl₃: δ = 8.37 – 8.32 (m, ArH, 1H), 7.49 (pt, ³J_{HH} = 7.5 Hz, ArH, 1H), 7.45 – 7.42 (m, ArH, 1H), 7.38 (d, ³J_{HH} = 7.5 Hz, ArH, 1H), 7.35 – 7.30 (m, ArH, 1H), 7.07 – 7.03 (m, ArH, 2H), 7.01 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 6.95 – 6.92 (m, ArH, 1H), 6.87 – 6.81 (m, ArH, 3H), 6.69 (d, ArH, ³J_{HH} = 8.5 Hz, 2H), 3.75 (s, O-CH₃, 3H).

¹³C-NMR (126 MHz) CDCl₃: δ = 161.5 (d, ¹J_{FC} = 246.0 Hz, ArC), 158.9 (ArC), 158.2 (ArC), 148.4 (ArC), 141.5 (ArC), 140.8 (ArC), 137.5 (ArC), 135.2 (ArC), 133.7 (ArC), 131.1 (d, ³J_{FC} = 7.8 Hz; 2 x ArC), 130.7 (2 x ArC), 128.6 (ArC), 129.1 (ArC), 128.2 (ArC), 126.9 (ArC), 126.6 (ArC), 121.0 (ArC), 114.5 (d, ²J_{FC} = 21.1 Hz; 2 x ArC), 113.2 (2 x ArC), 55.1 (O-CH₃).

HRMS-ESI (m/z) calculated for C₂₄H₁₈FNO [+H]⁺: 356.1445, found: 356.1444. LCMS purity (UV) = 93 %, t_R 16.35 min.

2-(4,4'-Fluorobiphenyl-2,6-yl)pyridine (**4.29**)

Product **4.29** was obtained as a viscous oil (0.012 g, 8%). The spectral data were concurrent with those reported.⁵

4.6.6 1-(4'-Trifluoromethylbiphenyl-2-yl)pyrrolidin-2-one (**4.30**)

The same method as that of **4.19** was used on a 0.3 mmol scale with 4-trifluoromethylbenzene diazonium tetrafluoroborate (1.2 mmol, 0.31 g). Product **4.30** was obtained as a viscous oil (0.081 g, 89%).

¹H-NMR (500 MHz) CDCl₃: δ = 7.68 – 7.64 (m, ArH, 2H), 7.50 (d, ³J_{HH} = 8.0 Hz, ArH, 2H), 7.46 – 7.41 (m, ArH, 1H), 7.40 – 7.36 (m, ArH, 1H), 7.35 – 7.32 (m, ArH, 1H), 7.26 – 7.25 (m, ArH, 1H), 3.27 (d, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.42 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.91 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). The spectral data were concurrent with those reported.

4.6.7 1-(3'-Trifluoromethylbiphenyl-2-yl)pyrrolidin-2-one (**4.31**)

The same method as that of **4.19** was used on a 0.3 mmol scale with 3-trifluoromethylbenzene diazonium tetrafluoroborate (1.2 mmol, 0.31 g). Product **4.31** was obtained as an oil (0.082 g, 90%).

¹H-NMR (500 MHz) CDCl₃: δ = 7.64 – 7.57 (m, ArH, 3H), 7.53 (pt, ³J_{HH} = 7.6 Hz, ArH, 1H), 7.47 – 7.42 (m, ArH, 1H), 7.42 – 7.39 (m, ArH, 2H), 7.33 (d, ³J_{HH} = 7.5 Hz, ArH, 1H), 3.28 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.40 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.91 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). The spectral data were concurrent with those reported.

4.6.8 1-(4'-Methylbiphenyl-2-yl)pyrrolidin-2-one (**4.32**)

The same method as that of **4.19** was used on a 0.3 mmol scale with 4-methylbenzene diazonium tetrafluoroborate (1.21 mmol, 0.25 g). Product **4.32** was obtained as an oil (0.051 g, 67%).

¹H-NMR (500 MHz) CDCl₃: δ = 7.40 – 7.33 (m, ArH, 4H), 7.31 – 7.28 (m, ArH, 1H), 7.25 – 7.24 (m, ArH, 1H), 7.19 (d, ³J_{HH} = 7.5 Hz, ArH, 2H), 3.20 (t, ³J_{HH} = 7.0 Hz,

COCH₂CH₂CH₂N, 2H), 2.42 (t, $^3J_{HH} = 8.0$ Hz, COCH₂CH₂CH₂N, 2H), 2.37 (s, CH₃, 3H), 1.87 (p, $^3J_{HH} = 7.5$ Hz, COCH₂CH₂CH₂N, 2H). The spectral data were concurrent with those reported.

4.6.9 1-(4'-Nitrobiphenyl-2-yl)pyrrolidin-2-one (**4.33**)

The same method as that of was used on a 3.5 mmol scale with 4-nitrobenzene diazonium tetrafluoroborate (11 mmol, 2.61 g). Product **4.33** was obtained as an oil (0.86 g, 87%).

¹H-NMR (500 MHz) CDCl₃: $\delta = 8.26$ (d, $^3J_{HH} = 9.0$ Hz, ArH, 2H), 7.54 (d, $^3J_{HH} = 9.0$ Hz, ArH, 2H), 7.51 – 7.46 (m, ArH, 1H), 7.42 (pt, $^3J_{HH} = 7.5$ Hz, ArH, 1H), 7.40 – 7.37 (m, ArH, 1H), 7.34 (d, $^3J_{HH} = 8.0$ Hz, ArH, 1H), 3.34 (t, $^3J_{HH} = 7.0$ Hz, COCH₂CH₂CH₂N, 2H), 2.40 (t, $^3J_{HH} = 8.0$ Hz, COCH₂CH₂CH₂N, 2H), 1.95 (p, $^3J_{HH} = 7.5$ Hz, COCH₂CH₂CH₂N, 2H). The spectral data were concurrent with those reported.⁸⁶

4.6.10 1-(4'-Hydroxybiphenyl-2-yl)pyrrolidin-2-one (**4.34**)

In a stirred solution of 1-(4'-methoxybiphenyl-2-yl)pyrrolidin-2-one (1.6 mmol, 0.42 g) in DCM (10mL) was added 1M BBr₃ (10 mL) in DCM dropwise at 0°C under inert atmosphere. The reaction mixture was allowed to warm to ambient temperature and stirred for additional 16 h. The resulting mixture was carefully quenched with saturated sodium bicarbonate (50 mL) and the mixture was extracted with DCM (40mL x 2). The combined organic layer was dried (MgSO₄) and concentrated under reduced pressure. The resulting crude product was triturated with diethyl ether overnight. The precipitate was collected by filtration to afford a grey solid (0.24 g, 58%)

¹H-NMR (500 MHz) DMSO-D₆: $\delta = 7.36 - 7.29$ (m, ArH, 3H), 7.26 – 7.22 (m, ArH, 1H), 7.10 (d, $^3J_{HH} = 8.7$ Hz, 2H), 6.81 – 6.76 (m, ArH, 2H), 3.19 (t, $^3J_{HH} = 7.0$ Hz, COCH₂CH₂CH₂N, 2H), 2.23 (t, $^3J_{HH} = 8.0$ Hz, COCH₂CH₂CH₂N, 2H), 1.81 (p, $^3J_{HH} = 7.5$ Hz, COCH₂CH₂CH₂N, 2H).

¹³C-NMR (126 MHz) DMSO-D₆: $\delta = 174.7$ (C=O), 157.3 (ArC), 137.3 (ArC), 139.5 (ArC), 136.9 (ArC), 130.9 (ArC), 129.8 (ArC), 129.5 (ArC x 2), 129.0 (ArC), 128.1 (ArC), 128.0 (ArC), 115.7 (ArC x 2), 49.9 (COCH₂CH₂CH₂N), 31.1 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N).

HRMS-ESI (m/z) calculated for $C_{16}H_{15}NO_2$ $[+H]^+$: 267.1259, found: 267.1262 LCMS purity (UV) = 99%, tR 18.51 min.

4.6.11 1-(4'-Aminobiphenyl-2-yl)pyrrolidin-2-one (4.36)

To a stirred solution of 1-(4'-nitrobiphenyl-2-yl)pyrrolidin-2-one (2.8 mmol, 0.8 g) in ethyl acetate (20 mL) was added tin(II) chloride dihydrate (14 mmol, 3.2 g) and the reaction was stirred at 70 °C overnight. The resulting mixture was neutralised with saturated sodium bicarbonate and extracted with ethyl acetate (40 mL x 2). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford the product as a white solid (0.62 g, 88%).

1H -NMR (500 MHz) DMSO- D_6 : δ = 7.34 – 7.24 (m, ArH, 3H), 7.20 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 1H), 6.96 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2H), 6.61 – 6.52 (m, ArH, 2H), 3.18 (t, $^3J_{HH}$ = 7.0 Hz, $COCH_2CH_2CH_2N$, 2H), 2.25 (t, $^3J_{HH}$ = 8.0 Hz, $COCH_2CH_2CH_2N$, 2H), 1.82 (p, $^3J_{HH}$ = 7.5 Hz, $COCH_2CH_2CH_2N$, 2H).

^{13}C -NMR (126 MHz) $CDCl_3$: δ = 175.7 (C=O), 145.9 (ArC), 139.6 (ArC), 136.2 (ArC), 130.8 (ArC), 130.8 (ArC), 129.3 (ArC x 2), 129.2 (ArC), 128.4 (ArC), 128.0 (ArC), 127.8 (ArC), 115.0 (ArC x 2), 49.9 ($COCH_2CH_2CH_2N$), 31.1 ($COCH_2CH_2CH_2N$), 19.0 ($COCH_2CH_2CH_2N$).

HRMS-ESI (m/z) calculated for $C_{16}H_{16}N_2O$ $[+H]^+$: 253.1335, found: 253.1328. LCMS purity (UV) = 95%, tR 13.38 min.

4.6.12 2-Chloro-N-[2'-(2-oxopyrrolidin-1-yl)biphenyl-4-yl]acetamide (4.37)

To a stirred solution of 1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one (0.38 mmol, 0.095 g) and triethylamine (0.38 mmol, 0.05 mL) in anhydrous DCM (8 mL) was added chloroacetyl chloride (0.46 mmol, 0.052 g) dropwise at 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure. The residue was washed with water

(10 mL x 3) and the resulting precipitate was collected by filtration to afford the final product as a white solid (0.093g, 75%).

$^1\text{H-NMR}$ (500 MHz) CDCl_3 : δ = 8.55 (s, **NH**, 1H), 7.59 (d, $^3J_{\text{HH}}$ = 8.1 Hz, **ArH**, 2H), 7.41 – 7.33 (m, **ArH**, 5H), 7.30 (d, $^3J_{\text{HH}}$ = 7.2 Hz, **ArH**, 1H), 4.17 (s, **COCH₂Cl**, 2H), 3.27 (t, $^3J_{\text{HH}}$ = 7.0 Hz, **COCH₂CH₂CH₂N**, 2H), 2.42 (t, $^3J_{\text{HH}}$ = 8.0 Hz, **COCH₂CH₂CH₂N**, 2H), 1.90 (p, $^3J_{\text{HH}}$ = 7.5 Hz, **COCH₂CH₂CH₂N**, 2H).

$^{13}\text{C-NMR}$ (126 MHz) CDCl_3 : δ = 175.7 (**CH₂NC=O**), 164.0 (**NHC=O**), 138.9 (**ArC**), 136.5 (**ArC**), 136.2 (**ArC**), 135.8 (**ArC**), 130.8 (**ArC**), 128.7 (**ArC** x 2), 128.3 (**ArC**), 128.2 (**ArC**), 119.9 (**ArC** x 2), 50.3 (**COCH₂CH₂CH₂N**), 43.0 (**COCH₂Cl**), 31.2 (**COCH₂CH₂CH₂N**), 19.0 (**COCH₂CH₂CH₂N**).

HRMS-ESI (m/z) calculated for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$ [$+\text{H}$] $^+$: 329.1051, found: 329.1053. LCMS purity (UV) = 97%, t_R 19.77 min.

4.6.13 2-Chloro-N-[2'-(2-oxopyrrolidin-1-yl)biphenyl-4-yl]acetamide (**4.38**)

To a stirred solution of 1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one (0.39 mmol, 0.10 g) and triethylamine (1.98 mmol, 0.20 g) in anhydrous DCM (10 mL) was added 3-chlorobenzoyl chloride (1.2 mmol, 0.21 g) and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (DCM/methanol over 0% - 10% gradient) to afford product **4.38** as a white amorphous solid (0.11 g, 72%).

4.38: $^1\text{H-NMR}$ (500 MHz) CDCl_3 : δ = 8.72 (s, **NH**, 1H), 7.95 – 7.90 (m, **ArH**, 1H), 7.79 (d, $^3J_{\text{HH}}$ = 7.5 Hz, **ArH**, 1H), 7.72 (d, $^3J_{\text{HH}}$ = 8.5 Hz, **ArH**, 2H), 7.50 (dd, $^3,^4J_{\text{HH}}$ = 8.0, 2.0 Hz, **ArH**, 1H), 7.40 – 7.34 (m, **ArH**, 6H), 7.32 – 7.26 (m, 1H), 3.31 (t, $^3J_{\text{HH}}$ = 7.0 Hz, **ArH**, **COCH₂CH₂CH₂N**, 2H), 2.38 (t, $^3J_{\text{HH}}$ = 8.0 Hz, **COCH₂CH₂CH₂N**, 2H), 1.91 (p, $^3J_{\text{HH}}$ = 7.5 Hz, **COCH₂CH₂CH₂N**, 2H).

$^{13}\text{C-NMR}$ (126 MHz) CDCl_3 : δ = 175.8 (**CH₂NC=O**), 164.6 (**NHC=O**), 139.1 (**ArC**), 137.8 (**ArC**), 136.6 (**ArC**), 136.1 (**ArC**), 135.1 (**ArC**), 134.7 (**ArC**), 131.8 (**ArC**), 130.9

(ArC), 129.9 (ArC), 128.9 (ArC x 2), 128.5 (ArC), 127.6 (ArC), 125.5 (ArC x 2), 50.5 (COCH₂CH₂CH₂N), 31.2 (COCH₂CH₂CH₂N), 18.9 (COCH₂CH₂CH₂N).

HRMS-ESI (m/z) calculated for C₂₃H₁₉ClN₂O₂ [$+H$]⁺: 391.1208, found: 391.1199. LCMS purity (UV) = 91 %, tR 18.38 min.

4.6.14 1-[2'-(2-oxopyrrolidin-1-yl)biphenyl-4-yl]1*H*-pyrrole-2,5-dione (**4.40**)

1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one (0.20 mmol, 0.050 g), maleic anhydride (0.24 mmol, 0.024 g) were dissolved in CHCl₃ (3 mL) and stirred for 2 h. The reaction mixture was concentrated under reduced pressure. To a stirred solution of the crude maleic acid in acetic anhydride (19.5 mmol, 2.0 g) was added sodium acetate (0.40 mmol, 0.033 g) and heated at reflux for 2 h. After cooling to ambient temperature, the reaction was quenched with water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The crude mixture was purified by column chromatography (hexane/ethyl acetate over 0% - 10% gradient) to afford **4.40** as a yellow solid (0.036g, 54%).

4.40: ¹H-NMR (500 MHz) CDCl₃: δ = 7.48 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 7.44 – 7.41 (m, ArH, 2H), 7.40 – 7.38 (m, ArH, 3H), 7.35 – 7.31 (m, ArH, 1H), 6.88 (s, COCHCHCO, 2H), 3.25 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.45 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.91 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H).

¹³C-NMR (126 MHz) CDCl₃: δ = 175.8 (CH₂NC=O), 169.4 (CHCONCOCH), 138.7 (ArC), 136.4 (ArC), 134.3 (ArC x 2), 130.8 (ArC), 130.7 (ArC), 129.1 (ArC x 2), 129.0 (ArC), 128.5 (ArC), 128.2 (ArC), 125.8 (ArC x 2), 50.3 (COCH₂CH₂CH₂N), 31.2 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N).

HRMS-ESI (m/z) calculated for C₂₀H₁₆N₂O₃ [$+H$]⁺: 333.1234, found: 333.1225. LCMS purity (UV) = 97 %, tR 18.77 min.

4.7 References

- 1 D. P. Curran, *Synthesis*, 1988, **1988**, 417–439.
- 2 C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, 1960, **82**, 6113–6115.
- 3 F. Recupero and C. Punta, *Chem. Rev.*, 2007, **107**, 3800–3842.
- 4 H. Amii and K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119–2183.
- 5 B. A. Arndtsen, R. G. Bergman, T. A. Mobley and T. H. Peterson, *Acc. Chem. Res.*, 1995, **28**, 154–162.
- 6 S. J. Blanksby and G. B. Ellison, *Acc. Chem. Res.*, 2003, **36**, 255–263.
- 7 A. S. Borovik, *Chem. Soc. Rev.*, 2011, **40**, 1870–1874.
- 8 J. M. Fraile, J. I. García, J. A. Mayoral and M. Roldán, *Org. Lett.*, 2007, **9**, 731–733.
- 9 H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417–424.
- 10 E. Clot, C. Mégret, O. Eisenstein and R. N. Perutz, *J. Am. Chem. Soc.*, 2009, **131**, 7817–7827.
- 11 D. Balcells, E. Clot and O. Eisenstein, *Chem. Rev.*, 2010, **110**, 749–823.
- 12 S. Potavathri, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. Lebris and B. Deboef, *J. Am. Chem. Soc.*, 2010, **132**, 14676–14681.
- 13 L. Ackermann and S. Fenner, *Org. Lett.*, 2011, **13**, 6548–6551.
- 14 S. H. Park, J. Kwak, K. Shin, J. Ryu, Y. Park and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 2492–2502.
- 15 M. E. Tauchert, C. D. Incarvito, A. L. Rheingold, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2012, **134**, 1482–1485.
- 16 K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430–11433.
- 17 Y. Li, X. S. Zhang, K. Chen, K. H. He, F. Pan, B. J. Li and Z. J. Shi, *Org. Lett.*, 2012, **14**, 636–639.
- 18 Y. Lian, R. G. Bergman, L. D. Lavis and J. A. Ellman, *J. Am. Chem. Soc.*, 2013, **135**, 7122–7125.
- 19 D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814–825.
- 20 Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301.
- 21 R. J. Tang, C. P. Luo, L. Yang and C. J. Li, *Adv. Synth. Catal.*, 2013, **355**, 869–

- 873.
- 22 H. Y. Thu, W. Y. Yu and C. M. Che, *J. Am. Chem. Soc.*, 2006, **128**, 9048–9049.
 - 23 Z. Ke and T. R. Cundari, *Organometallics*, 2010, **29**, 821–834.
 - 24 B. Xiao, T. J. Gong, J. Xu, Z. J. Liu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1466–1474.
 - 25 D. Zhu, G. Yang, J. He, L. Chu, G. Chen, W. Gong, K. Chen, M. D. Eastgate and J. Q. Yu, *Angew. Chem. Int. Ed.*, 2015, **54**, 2497–2500.
 - 26 W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7603–7610.
 - 27 J. Park and S. Chang, *Angew. Chem. Int. Ed.*, 2015, **54**, 14103–14107.
 - 28 K. H. Ng, F. N. Ng and W. Y. Yu, *Chem. Commun.*, 2012, **48**, 11680–11682.
 - 29 X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li and H. Ge, *Nat. Commun.*, 2015, **6**, 6462–6472.
 - 30 C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2013, **15**, 3014–3017.
 - 31 K. H. Ng, Z. Zhou and W. Y. Yu, *Chem. Commun.*, 2013, **49**, 7031–7033.
 - 32 C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2012, **14**, 656–659.
 - 33 H. Wang and F. Glorius, *Angew. Chemie - Int. Ed.*, 2012, **51**, 7318–7322.
 - 34 N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449–6457.
 - 35 B. J. Li, H. Y. Wang, Q. L. Zhu and Z. J. Shi, *Angew. Chem. Int. Ed.*, 2012, **51**, 3948–3952.
 - 36 N. S. Upadhyay, V. H. Thorat, R. Sato, P. Annamalai, S.C. Chuang and C. H. Cheng, *Green Chem.*, 2017, **19**, 3219–3224.
 - 37 H. Chen, S. Schlecht, T. C. Semple and J. F. Hartwig, *Science.*, 2000, **287**, 1995–1997.
 - 38 J. F. Hartwig, *Acc. Chem. Res.*, 2012, **45**, 864–873.
 - 39 P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918.
 - 40 S. Oi, Y. Tanaka and Y. Inoue, *Organometallics*, 2006, **25**, 4773–4778.
 - 41 G. Onodera, H. Imajima, M. Yamanashi, Y. Nishibayashi, M. Hidai and S. Uemura, *Organometallics*, 2004, **23**, 5841–5848.
 - 42 N. A. Foley, M. Lait, J. P. Lee, T. B. Gunnoe, T. R. Cundari and J. L. Petersen, *J. Am. Chem. Soc.*, 2007, **129**, 6765–6781.
 - 43 D. H. Lee, K. H. Kwon and C. S. Yi, *Science*, 2011, **333**, 1613–1616.

- 44 T. Kochi, S. Urano, H. Seki, E. Mizushima, M. Sato and F. Kakiuchi, *J. Am. Chem. Soc.*, 2009, **131**, 2792–2793.
- 45 S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **366**, 529–531.
- 46 U. Helmstedt and E. Clot, *Chem. Eur. J.*, 2012, **18**, 11449–11458.
- 47 J. Le Bras and J. Muzart, *Chem. Rev.*, 2011, **111**, 1170–1214.
- 48 S. Kakiuchi, F. Sato, T. Tsujimoto, T. Yamauchi, M. Chatani, N. Murai, *Chem. Lett.*, 1998, **27**, 1053–1054.
- 49 O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298–19301.
- 50 N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877–5884.
- 51 C. J. Teskey, A. Y. W. Lui and M. F. Greaney, *Angew. Chem. Int. Ed.*, 2015, **54**, 11677–11680.
- 52 Q. Yu, L. Hu, Y. Wang, S. Zheng and J. Huang, *Angew. Chem. Int. Ed.*, 2015, **54**, 15284–15288.
- 53 Z. Fan, J. Ni and A. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 8470–8475.
- 54 Z. Fan, J. Li, H. Lu, D. Y. Wang, C. Wang, M. Uchiyama and A. Zhang, *Org. Lett.*, 2017, **19**, 3199–3202.
- 55 B. Li, S. L. Fang, D. Y. Huang and B. F. Shi, *Org. Lett.*, 2017, **19**, 3950–3953.
- 56 C. C. Yuan, X. L. Chen, J. Y. Zhang and Y. S. Zhao, *Org. Chem. Front.*, 2017, **4**, 1867–1871.
- 57 C. Yuan, L. Zhu, R. Zeng, Y. Lan and Y. Zhao, *Angew. Chem. Int. Ed.*, 2018, **57**, 1277–1281.
- 58 J. A. Leitch, C. L. McMullin, A. J. Paterson, M. F. Mahon, Y. Bhonoah and C. G. Frost, *Angew. Chem. Int. Ed.*, 2017, **56**, 15131–15135.
- 59 J. Kim, J. Kim and S. Chang, *Chem. Eur. J.*, 2013, **19**, 7328–7333.
- 60 M. Bhanuchandra, M. Ramu Yadav, R. K. Rit, M. Rao Kuram and A. K. Sahoo, *Chem. Commun.*, 2013, **49**, 5225–5227.
- 61 M. R. Yadav, R. K. Rit and A. K. Sahoo, *Org. Lett.*, 2013, **15**, 1638–1641.
- 62 V. S. Thirunavukkarasu, K. Raghuvanshi and L. Ackermann, *Org. Lett.*, 2013, **15**, 3286–3289.
- 63 Y. Shin, S. Han, U. De, J. Park, S. Sharma, N. K. Mishra, E. K. Lee, Y. Lee, H. S. Kim and I. S. Kim, *J. Org. Chem.*, 2014, **79**, 9262–9271.
- 64 J. Gui, Q. Zhou, C. M. Pan, Y. Yabe, A. C. Burns, M. R. Collins, M. A. Ornelas,

- Y. Ishihara and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 4853–4856.
- 65 X. Chen, K. M. Engle, D.-H. Wang and J. Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094–5115.
- 66 M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J. L. Peglion, E. Clot and O. Baudoin, *J. Am. Chem. Soc.*, 2008, **130**, 15157–15166.
- 67 N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 11234–11241.
- 68 A. Mukherjee, T. K. Sen, P. K. Ghorai and S. K. Mandal, *Organometallics*, 2013, **32**, 7213–7224.
- 69 J. Spencer, D. P. Sharratt, J. Dupont, A. L. Monteiro, V. I. Reis, M. P. Stracke, F. Rominger and I. M. McDonald, *Organometallics*, 2005, **24**, 5665–5672.
- 70 L. M. Mirica and J. R. Khusnutdinova, *Coord. Chem. Rev.*, 2013, **257**, 299–314.
- 71 C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633–639.
- 72 J. M. Racowski, N. D. Ball and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18022–18025.
- 73 M. Lafrance, C. N. Rowley, T. K. Woo and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 8754–8756.
- 74 T. Yagyu, M. Hamada, K. Osakada and T. Yamamoto, *Organometallics*, 2001, **20**, 1087–1101.
- 75 J. R. Khusnutdinova, N. P. Rath and L. M. Mirica, *J. Am. Chem. Soc.*, 2010, **132**, 7303–7305.
- 76 M. H. Pérez-Temprano, J. M. Racowski, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2014, **136**, 4097–4100.
- 77 Z. Dong and G. Dong, *J. Am. Chem. Soc.*, 2013, **135**, 18350–18353.
- 78 A. Martins, B. Mariampillai and M. Lautens, *Top. Curr. Chem.*, 2010, **292**, 1–33.
- 79 Y. H. Zhang, B. F. Shi and J. Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 5072–5074.
- 80 A. N. Campbell and S. S. Stahl, *Acc. Chem. Res.*, 2012, **45**, 851–863.
- 81 Y. Izawa and S. S. Stahl, *Adv. Synth. Catal.*, 2010, **352**, 3223–3229.
- 82 A. N. Campbell, P. B. White, I. A. Guzei and S. S. Stahl, *J. Am. Chem. Soc.*, 2010, **132**, 15116–15119.
- 83 K. J. Stowers, A. Kubota and M. S. Sanford, *Chem. Sci.*, 2012, **3**, 3192–3195.
- 84 A. N. Vedernikov, *Acc. Chem. Res.*, 2012, **45**, 803–813.
- 85 J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4762.
- 86 D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, *J. Am. Chem.*

- Soc.*, 2011, **133**, 18566–18569.
- 87 K. Hong, H. Park and J.Q. Yu, *ACS Catal.*, 2017, **7**, 6938–6941.
 - 88 P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K. S. Yeung and J. Q. Yu, *Nature*, 2017, **551**, 489–493.
 - 89 Y. Nakao, N. Kashiwara, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2008, **130**, 16170–16171.
 - 90 L. McMurray, F. O’Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885–1898.
 - 91 M. Brzozowski, J. A. Forni, G. Paul Savage and A. Polyzos, *Chem. Commun.*, 2015, **51**, 334–337.
 - 92 T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.*, 2011, **40**, 1910–1925.
 - 93 M. Moselage, J. Li and L. Ackermann, *ACS Catal.*, 2016, **6**, 498–525.
 - 94 D. Zell, Q. Bu, M. Feldt and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 7408–7412.
 - 95 S. Nakanowatari, R. Mei, M. Feldt and L. Ackermann, *ACS Catal.*, 2017, **7**, 2511–2515.
 - 96 K. Gao, P. S. Lee, T. Fujita and N. Yoshikai, *J. Am. Chem. Soc.*, 2010, **132**, 12249–12251.
 - 97 N. Barbero, R. SanMartin and E. Domínguez, *Org. Biomol. Chem.*, 2010, **8**, 841–845.
 - 98 W. Xu, J. Shen, C. A. Dunn, S. Desai and M. J. Bessman, *Mol. Microbiol.*, 2001, **39**, 286–290.
 - 99 D. I. Fisher, J. L. Cartwright, H. Harashima, H. Kamiya and A. G. McLennan, *BMC Biochem.*, 2004, **5**, 1–24.
 - 100 A. G. McLennan, *Cell. Mol. Life Sci.*, 2006, **63**, 123–143.
 - 101 T. Gabaldón, *Cell. Mol. Life Sci.*, 2014, **71**, 2373–2376.
 - 102 D. Speijer, *Bioessays*, 2011, **33**, 88–94.
 - 103 M. C. Hunt, V. Tillander and S. E. H. Alexson, *Biochimie*, 2014, **98**, 45–55.
 - 104 R. Ofman, D. Speijer, R. Leen and R. J. A. Wanders, *Biochem. J.*, 2006, **393**, 537–543.
 - 105 S. J. Reilly, V. Tillander, R. Ofman, S. E. H. Alexson and M. C. Hunt, *J. Biochem.*, 2008, **144**, 655–663.
 - 106 S. R. Abdelraheim, D. G. Spiller and A. G. McLennan, *Biochem. J.*, 2003, **374**, 329–335.
 - 107 L. Gasmi and A. G. McLennan, *Biochem. J.*, 2001, **357**, 33–38.

- 108 A. E. Gylfe, R. Katainen, J. Kondelin, T. Tanskanen, T. Cajuso, U. Hänninen, J. Taipale, M. Taipale, L. Renkonen-Sinisalo, H. Järvinen, J. P. Mecklin, O. Kilpivaara, E. Pitkänen, P. Vahteristo, S. Tuupanen, A. Karhu and L. A. Aaltonen, *PLoS Genet.*, DOI:10.1371/journal.pgen.1003876.
- 109 S. A. Shumar, P. Fagone, A. Alfonso-Pecchio, J. T. Gray, J. E. Rehg, S. Jackowski and R. Leonardi, *PLoS One*, DOI:10.1371/journal.pone.0130013.
- 110 D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18566–18569.
- 111 A. W. Hung, H. L. Silvestre, S. Wen, A. Ciulli, T. L. Blundell and C. Abell, *Angew. Chem. Int. Ed.*, 2009, **48**, 8452–8456.
- 112 N. Howard, C. Abell, W. Blakemore, G. Chessari, M. Congreve, S. Howard, H. Jhoti, C. W. Murray, L. C. A. Seavers and R. L. M. Van Montfort, *J. Med. Chem.*, 2006, **49**, 1346–1355.
- 113 B. J. Davis and S. D. Roughley, in *Annual Reports in Medicinal Chemistry*, 2017, vol. 50, pp. 263–299.
- 114 M. Mondal, M. Y. Unver, A. Pal, M. Bakker, S. P. Berrier and A. K. H. Hirsch, *Chem. Eur. J.*, 2016, **22**, 14826–14830.
- 115 S. Zhao and H. Li, in *Epigenetic Technological Applications*, 2015, pp. 125–147.
- 116 R. Scoffin and M. Slater, *Drug Discov. Dev. Deliv.*, 2015, **7**, 2–5.
- 117 J. J. Barker, O. Barker, S. M. Courtney, M. Gardiner, T. Hesterkamp, O. Ichihara, O. Mather, C. A. G. N. Montalbetti, A. Müller, M. Varasi, M. Whittaker and C. J. Yarnold, *Chem. Med. Commun.*, 2010, **5**, 1697–1700.
- 118 D. J. Jollow, J. R. Mitchell, W. Z. Potter, D. C. Davis, J. R. Gillette and B. B. Brodie, *J. Pharmacol. Exp. Ther.*, 1973, **187**, 195–202.
- 119 D. Gunnell, V. Murray and K. Hawton, *Suicide Life. Threat. Behav.*, 2000, **30**, 313–326.
- 120 I. S. Dunn, D. J. Liberato, N. Castagnoli and V. S. Byers, *Cell. Immunol.*, 1982, **74**, 220–233.
- 121 V. R. Thompson and A. P. Decaprio, *Chem. Res. Toxicol.*, 2013, **26**, 1263–1271.
- 122 I. M. Serafimova, M. A. Pufall, S. Krishnan, K. Duda, M. S. Cohen, R. L. Maglathlin, J. M. McFarland, R. M. Miller, M. Frödin and J. Taunton, *Nat. Chem. Biol.*, 2012, **8**, 471–476.
- 123 J. C. Powers, J. L. Asgian, Ö. D. Ekici and K. E. James, *Chem. Rev.*, 2002, **102**, 4639–4750.

Chapter 5

N1-Arylation of 1,4-Benzodiazepin-2-ones with Diaryliodonium Salts

5.1 Introduction

Compounds containing a 1,4-benzodiazepine scaffold are often termed as ‘privileged structures’ and are of significant interest to organic and medicinal chemists.^{1–18} Many bioactive 1,4- benzodiazepines include *N*-arylated benzodiazepines; for example, the benzodiazepine derivative, **A** (Figure 5.1), is a bradykinin antagonist¹⁹ and the related benzotriazepine **B** is an antagonist at the parathyroid hormone (PTH)-1 receptor.²⁰ Typically *N*-arylated benzodiazepines can be prepared by transition-metal catalysed couplings, often with copper, with various arylating agents. Generally, the reaction scope is limited with these routes and often require high temperatures and strong bases.^{19,21–23}

Being able to generate libraries of diverse analogues, in this case by adding N-H functionality to a privileged core unit, using mild and efficient methodologies, can substantially improve SAR studies (structure – activity relationship) and optimise the drug development process potentially to repurposing privileged scaffolds for new biological targets.^{24,25}

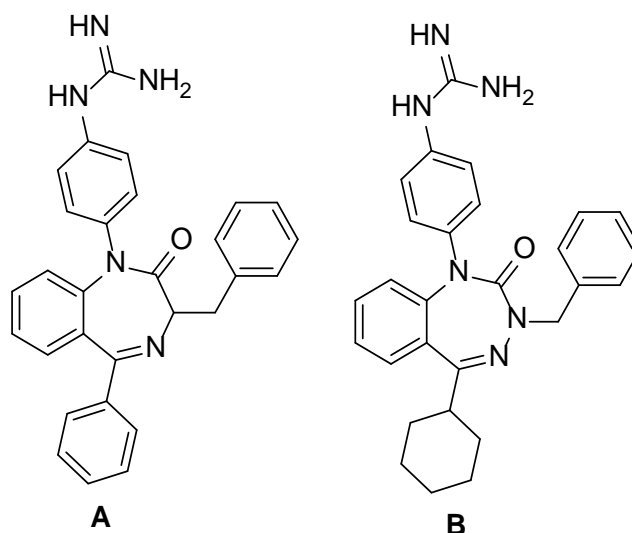
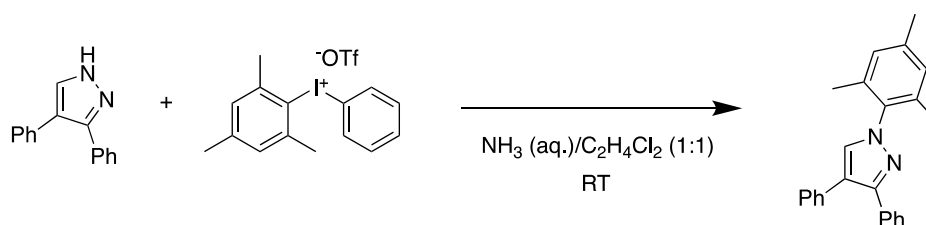


Figure 5.1: Bioactive *N*-arylated benzodiazepine and benzotriazepine

5.2 Results and discussion

As apparent from Chapter 2 and 3, we have an active interest in benzodiazepines,^{26,27} where protocols to functionalise 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones via a late-stage palladacycle assisted ortho C-H activation protocol have been reported.^{28,29} In this Chapter, our approach to generate a series of *NI*-arylated 1,4-benzodiazepines using diaryliodonium salts is presented. The latter react with nucleophiles in the absence of transition metal catalysts and are commonly used in organic synthesis as electrophilic reagents.^{30–35}

Novak *et al.* recently reported a protocol for the *N*-arylation of pyrazoles.³⁶



Scheme 5.1: *N*-arylation of pyrazoles

A quick screen of conditions, adapting this protocol using diaryliodonium salts with weak bases under mild conditions, showed that it was indeed possible to perform similar arylations on the 1,4-benzodiazepine system. Upon initial screening of a number of solvents, DCE (1,2-dichloroethane) was found to give the best results (Table 5.1, Entry 2). Solvents such as PEG (polypropylene glycol) and acetic acid gave poor yields. Similar results were observed on pyrazoles by Novak *et al.* where apolar solvents, immiscible in water, produced the best results.

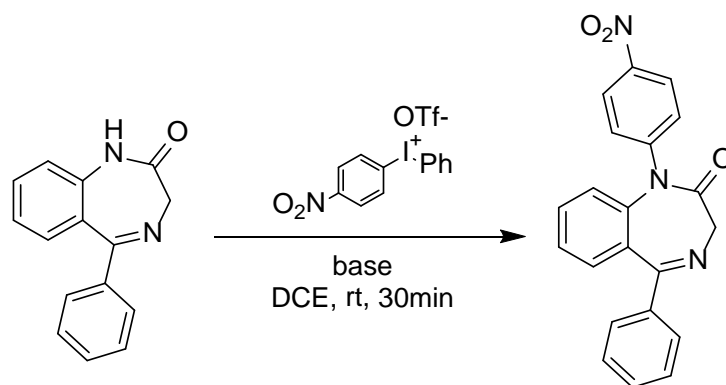
Table 5.1: Optimisation of N-arylation of 1,4-benzodiazepines – solvent effects

Entry	Solvent	Conversion % ^a
1	Toluene	95
2	DCE	99
3	PEG	-
4	AcOH	-
5	Chloroform	85

^a LCMS conversion

A number of bases were tested subsequently and both NH₃ (25% w/w) and NaOH (sat. aq.) gave similar and the best results (Table 2, entry 1, 2).

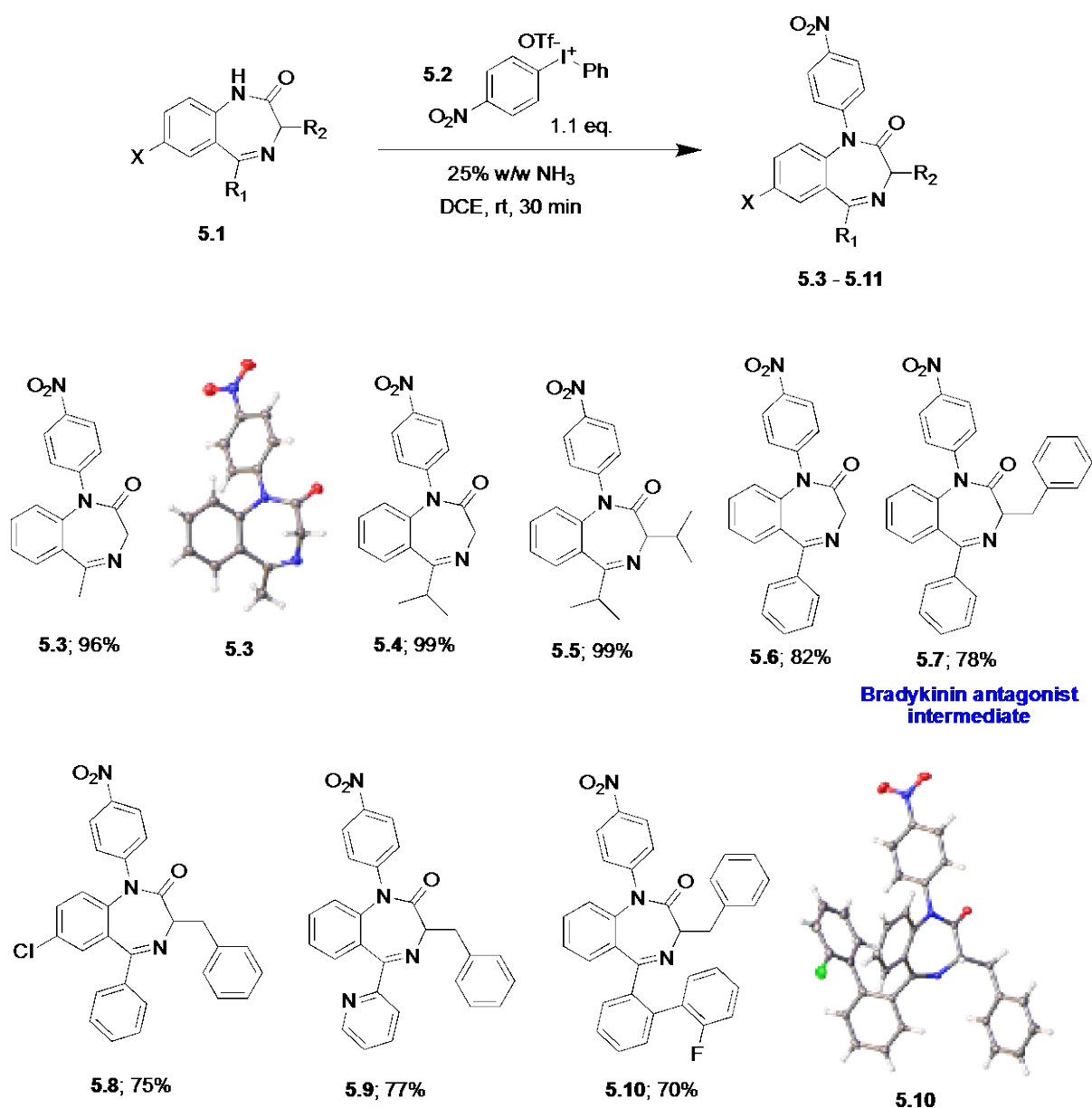
Table 5.2: Optimisation of N-arylation of 1,4-benzodiazepines – base effects



Entry	Base	Conversion % ^a
1	NaOH (sat. aq.)	99
2	NH ₃ (25% w/w)	99
3	K ₂ CO ₃	80
4	NaH	-

^a LCMS conversion

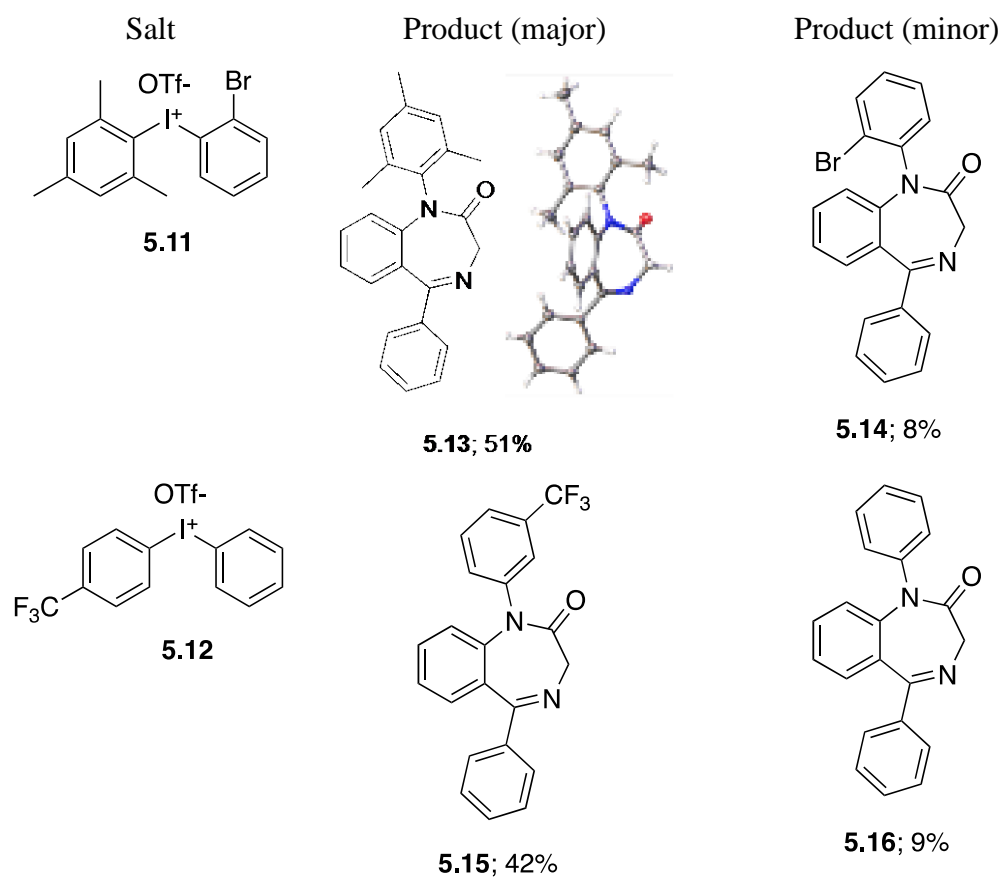
Hence, optimal conditions appeared to use NH₃ (aq.), DCE at room temperature for 30 min. Next, a series of functionalized 1,4-benzodiazepines was *N*-arylated using (4-nitrophenyl)phenyliodonium triflate in good to excellent yields (Scheme 5.2). Generally, in transition-metal-free processes unsymmetrical diaryliodonium salts give a mixture of products where both aryl groups are transferred and the transfer of more sterically hindered and electron withdrawing group is preferable.³⁴ However, in this case (Scheme 5.1) only the nitrophenyl-group was transferred. We were able to *N*-arylate quite sterically hindered benzodiazepines such as **5.7**, **5.8** and **5.9**. Of note, **5.7** is a key intermediate towards **A**, the bradykinin B₂ receptor antagonist. We were also pleased to be able to conduct *N*-arylation on a previously ortho-arylated hindered benzodiazepine, **5.10**, in good yield, whose structure was also confirmed by X-ray crystallography. Such molecules may be useful precursors to e.g., alpha-helical mimetics in medicinal chemistry.^{37,38}

Scheme 5.2: *N*-arylated 1,4-benzodiazepines

The use of other unsymmetrical diaryliodonium triflates was also explored (Table 5.3), which required longer reaction time and led to both aryl groups being transferred to obtain **5.13** – **5.16**. As expected, the transfer of more sterically hindered or less electron rich groups was preferred. Further attempt to use unsymmetrical diaryliodonium salts such as phenyl(3-methylphenyl)iodonium triflate, phenyl(4-methylphenyl)iodonium triflate and (2-methylphenyl)(2,4,6-trimethylphenyl)iodonium triflate gave little or no products. Moreover, attempted *N*-arylation with symmetrical diaryliodonium triflates or

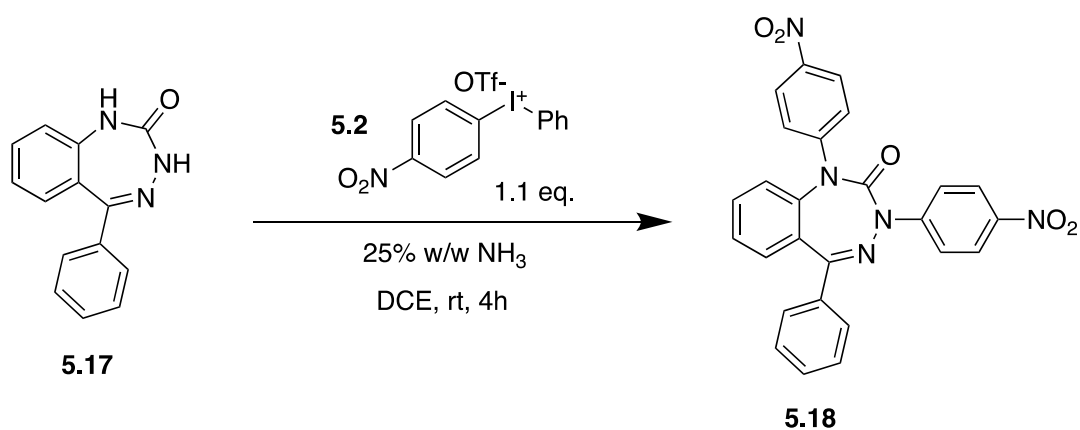
tetrafluoroborates such as bis(2-fluorophenyl)iodonium tetrafluoroborate and bis(4-bromophenyl)iodonium triflate, gave no products.

Table 5.3: Further *N*-arylation of 1,4-benzodiazepines



^a Reaction time 8h

We have briefly explored the *N*-arylation on a 1,3,4-benzotriazepine, **5.17**, which resulted in di-arylation and yielded **5.18** (Scheme 5.3).

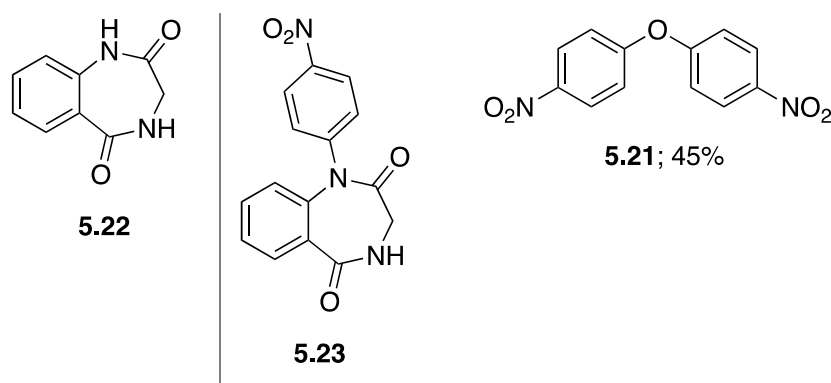


Scheme 5.3: N-arylation on a 1,3,4-Benzotriazepine

Interestingly, the iodonium salts were observed to undergo reaction with water present in the reaction to give diarylether products. The ether product is only observed when the benzodiazepine substrates react poorly with the diaryliodonium salts (Table 5.4). The ether product is also obtained merely by stirring the iodonium salt with water in DCE with a mild base for 20 min at room temperature with a yield of 43%. Olofsson *et al.* have reported the synthesis of related diarylethers by reacting diaryliodonium salts with phenols in the presence of mild bases.³⁹

Table 5.4: Ether formation

Substrate	Expected product	Observed product
<p>5.19</p>	<p>5.20</p>	<p>5.21; 43%</p>



5.3 Conclusion

In summary, we have presented a mild metal-free route to N-arylated benzodiazepines, three of which were structurally characterized in the solid state (**5.3**, **5.10**, **5.13**, with CCDC numbers 1560492-1560494 respectively.⁴⁰

5.4 Experimental details for Chapter 5

General experimental details are provided in Chapter 2.4.

5.4.2 General Procedure

To a stirred solution of the appropriate 1,4-benzodiazepine or 1,3,4-benzotriazepine (0.030 mmol – 1.00 mmol, 1 eq.) and diaryliodonium salt (0.033 – 1.10 mmol, 1.1 eq.) in DCE (5 – 10 mL) was added 25% w/w NH₃ solution (aq. 5 - 10 mL) and the reaction mixture was stirred for 30 min. (unless stated otherwise). Upon completion, the reaction mixture was diluted with dichloromethane (3x15 mL) and the layers were separated. Combined organic layers were dried (MgSO₄), concentrated under reduced pressure and purified by column chromatography, hexane/ethyl acetate (80:20 to 30:70).

5.4.3 1-(4-Nitrophenyl)-5-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.3**)

The product was obtained as white solid (0.60 mmol scale, 170 mg, 96%).

^1H -NMR (500 MHz) CDCl_3 : δ = 8.27 – 8.21 (m, ArH, 2H), 7.62 (dd, $^3J_{\text{HH}}$ = 7.5, 1.5 Hz, ArH, 1H), 7.40 – 7.35 (m, ArH, 3H), 7.34 – 7.29 (m, ArH, 1H), 6.82 (d, $^3J_{\text{HH}}$ = 8.0 Hz, ArH, 1H), 4.70 (d, $^2J_{\text{HH}}$ = 10.5 Hz, COCH_2 , 1H), 3.83 (d, $^2J_{\text{HH}}$ = 10.5 Hz, COCH_2 , 1H), 2.62 (s, CH_3 , 3H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 170.1 (C=O), 168.1 (C=N), 146.7 (ArC), 146.0 (ArC), 140.8 (ArC), 131.4 (ArC), 131.3 (ArC), 128.7 (ArC x 2), 127.8 (ArC), 125.9 (ArC), 125.1 (ArC), 124.5 (ArC x 2), 56.6 (COCH_2), 25.5 (CH_3).

HRMS-ESI (m/z) calculated for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$ [$+\text{H}$] $^+$: 296.1030, found: 296.1033. LCMS purity (UV) = 100%, tR 8.10 min.

5.4.4 1-(4-Nitrophenyl)-5-(propan-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.4**)

The product was obtained as a white solid (0.52 mmol scale, 166 mg, 99%).

^1H -NMR (500 MHz) CDCl_3 : δ = 8.27 – 8.20 (m, ArH, 2H), 7.59 (dd, $^3J_{\text{HH}}$ = 7.5, 2.0 Hz, ArH, 1H), 7.39 – 7.35 (m, ArH, 3H), 7.34 – 7.30 (m, ArH, 1H), 6.83 (dd, $^3J_{\text{HH}}$ = 8.0, 1.5 Hz, ArH, 1H), 4.72 (d, $^2J_{\text{HH}}$ = 10.5 Hz, COCH_2 , 1H), 3.82 (d, $^2J_{\text{HH}}$ = 10.5 Hz, COCH_2 , 1H), 3.34 – 3.25 (m, 1H), 1.35 (d, $^3J_{\text{HH}}$ = 7.0 Hz, $\text{CNCHC}_2\text{CH}_6$, 3H), 1.11 (d, $^3J_{\text{HH}}$ = 7.0 Hz, $\text{CNCHC}_2\text{CH}_6$, 3H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 176.9 (C=O), 168.7 (C=N), 146.7 (ArC), 145.9 (ArC), 141.5 (ArC), 131.6 (ArC), 130.9 (ArC), 128.3 (ArC x 2), 127.0 (ArC), 126.0 (ArC), 125.0 (ArC), 124.5 (ArC x 2), 56.5 (COCH_2), 35.6 (CNCHC_2H_6), 22.0 (CNCHC_2H_6), 19.2 (CNCHC_2H_6).

HRMS-ESI (m/z) calculated for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3$ [$+\text{H}$] $^+$: 324.1270, found: 324.1281. LCMS purity (UV) = 96 %, tR 18.73 min.

5.4.5 1-(4-Nitrophenyl)-3-(propan-2-yl)-5-(propan-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.5**)

The product was obtained as white solid (0.25 mmol scale, 91 mg, 99%).

$^1\text{H-NMR}$ (500 MHz) CDCl_3 : δ = 8.25 – 8.18 (m, ArH, 2H), 7.61 (dd, $^3J_{\text{HH}}$ = 8.0, 1.5 Hz, ArH, 1H), 7.39 – 7.24 (m, ArH, 4H), 6.85 (dd, J = 8.0, 1.5 Hz, ArH, 1H), 3.27 (hept, $^3J_{\text{HH}}$ = 7.0 Hz, CNCHCH₃CH₃, 1H), 3.12 (d, $^3J_{\text{HH}}$ = 9.5 Hz, COCHCHC₂H₆, 1H), 2.72 – 2.61 (m, COCHCHC₂H₆, 1H), 1.33 (d, $^3J_{\text{HH}}$ = 7.0 Hz, CNCHC₂H₆, 3H), 1.07 (d, $^3J_{\text{HH}}$ = 7.0 Hz, CNCHC₂H₆, 3H), 1.05 – 1.02 (m, COCHCHC₂H₆, 6H).

$^{13}\text{C-NMR}$ (126 MHz) CDCl_3 : δ = 173.9 (C=O), 168.3 (C=N), 147.4 (ArC), 145.7 (ArC), 141.1 (ArC), 131.9 (ArC), 130.6 (ArC), 128.4 (ArC x 2), 126.8 (ArC), 125.7 (ArC), 125.1 (ArC), 124.4 (ArC x 2), 69.3 (COCHCHC₂H₆), 35.5 (CNCHCH₃CH₃), 22.2 (COCHCHC₂H₆), 21.9 (CNCHC₂H₆), 20.1, (CNCHC₂H₆) 19.3 (COCHCHC₂H₆), 18.7 (COCHCHC₂H₆).

HRMS-ESI (m/z) calculated for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_3$ [$+\text{H}$] $^+$: 366.1812, found: 366.1816. LCMS purity (UV) = 95%, tR 23.47 min.

5.4.6 1-(4-Nitrophenyl)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.6**)

The product was obtained as white solid (0.60 mmol scale, 176 mg, 82%).

$^1\text{H-NMR}$ (500 MHz) CDCl_3 : δ = 8.30 – 8.23 (m, ArH, 2H), 7.77 – 7.71 (m, ArH, 2H), 7.55 – 7.51 (m, ArH, 1H), 7.49 – 7.45 (m, ArH, 3H), 7.45 – 7.41 (m, ArH, 3H), 7.29 (d, $^3J_{\text{HH}}$ = 8.0 Hz, ArH, 1H), 6.94 (d, $^3J_{\text{HH}}$ = 8.0 Hz, ArH, 1H), 4.96 (d, $^2J_{\text{HH}}$ = 10.5 Hz, COCH₂, 1H), 4.03 (d, $^2J_{\text{HH}}$ = 10.5 Hz, COCH₂, 1H).

$^{13}\text{C-NMR}$ (126 MHz) CDCl_3 : δ = 170.3 (C=O), 168.3 (C=N), 146.7 (ArC), 146.0 (ArC), 142.7 (ArC), 138.4 (ArC), 131.4 (ArC), 130.8 (ArC), 130.4 (ArC), 130.3 (ArC), 129.4 (ArC x 2), 128.5 (ArC x 2), 128.4 (ArC x 2), 125.4 (ArC), 125.0 (ArC), 124.5 (ArC x 2), 57.4 (COCH₂).

HRMS-ESI (m/z) calculated for $C_{21}H_{15}N_3O_3$ $[+H]^+$: 358.1186, found: 358.1187. LCMS purity (UV) = 95%, tR 18.35 min.

5.4.7 1-(4-Nitrophenyl)-3-benzyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.7**)

The product was obtained as white solid (0.40 mmol scale, 140 mg, 78%).

1H -NMR (500 MHz) $CDCl_3$: δ = 8.27 – 8.21 (m, ArH, 2H), 7.67 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2H), 7.52 – 7.48 (m, 1H), 7.47 – 7.43 (m, ArH, 2H), 7.41 – 7.37 (m, ArH, 5H), 7.36 – 7.30 (m, ArH, 3H), 7.25 – 7.21 (m, ArH, 2H), 6.90 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1H), 4.01 (dd, J = 7.5, 6.0 Hz, COCHCH₂, 1H), 3.68 (dd, $^{2,3}J_{HH}$ = 14.0, 6.0 Hz, COCHCH₂, 1H), 3.62 (dd, $^{2,3}J_{HH}$ = 14.0, 7.5 Hz, COCHCH₂, 1H).

^{13}C -NMR (126 MHz) $CDCl_3$: δ = 168.8 (C=O), 168.5 (C=N), 147.1 (ArC), 145.9 (ArC), 142.1 (ArC), 138.9 (ArC), 138.4 (ArC), 131.5 (ArC), 130.8 (ArC), 130.5 (ArC), 130.3 (ArC), 130.0 (ArC x 2), 129.5 (ArC x 2), 128.6 (ArC x 2), 128.5 (ArC x 2), 128.3 (ArC x 2), 126.3 (ArC), 125.3 (ArC), 125.1 (ArC), 124.5 (ArC x 2), 65.6 (COCHCH₂), 37.9 (COCHCH₂).

HRMS-ESI (m/z) calculated for $C_{28}H_{21}N_3O_3$ $[+H]^+$: 448.1656, found: 448.1669. LCMS purity (UV) = 99 %, tR 20.81 min.

5.4.8 7-Chloro-1-(4-nitrophenyl)-3-benzyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.8**)

The product was obtained as white solid (0.15 mmol scale, 54 mg, 75%).

1H -NMR (500 MHz) $CDCl_3$: δ = 8.26 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 2H), 7.66 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2H), 7.57 – 7.50 (m, ArH, 1H), 7.51 – 7.44 (m, ArH, 2H), 7.42 – 7.36 (m, ArH, 3H), 7.34 – 7.30 (m, ArH, 2H), 7.26 (s, ArH, 3H), 7.17 (d, J = 8.7 Hz, ArH, 1H), 6.85 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 1H), 3.99 (dd, J = 7.5, 6.0 Hz, COCHCH₂, 1H), 3.70 – 3.57 (m, COCHCH₂, 2H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 168.4, (C=O), 167.2 (C=N), 146.6 (ArC), 146.1 (ArC), 140.6 (ArC), 138.6 (ArC), 137.7 (ArC), 131.7 (ArC), 131.1 (ArC), 129.9 (ArC x 2), 129.8 (ArC), 129.5 (ArC x 2), 128.7 (ArC x 2), 128.6 (ArC x 2), 128.3 (ArC x 2), 126.5 (ArC), 126.4 (ArC), 126.2 (ArC), 124.6 (ArC x 2), 119.3 (ArC) 65.8 (COCHCH₂), 37.9 (COCHCH₂).

HRMS-ESI (m/z) calculated for $\text{C}_{28}\text{H}_{20}\text{ClN}_3\text{O}_3$ [$+\text{H}$]⁺: 482.1266, found: 482.1286. LCMS purity (UV) = 95%, tR 19.71 min.

5.4.9 1-(4-Nitrophenyl)-3-benzyl-5-(pyridine-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.9**)

The product was obtained as white solid (0.11 mmol scale, 38 mg, 77%).

^1H -NMR (500 MHz) CDCl_3 : δ = 8.67 – 8.62 (m, ArH, 1H), 8.15 (d, $^3J_{\text{HH}}$ = 8.0 Hz, ArH, 2H), 8.18 – 8.12 (m, ArH, 1H), 7.88 – 7.81 (m, ArH, 1H), 7.44 – 7.42 (m, ArH, 2H), 7.42 – 7.37 (m, ArH, 4H), 7.35 – 7.26 (m, ArH, 3H), 7.25 – 7.21 (m, ArH, 2H), 6.89 (d, $^3J_{\text{HH}}$ = 8.0 Hz, ArH, 1H), 4.10 (dd, $^3J_{\text{HH}}$ = 8.0, 6.0 Hz, COCHCH₂, 1H), 3.70 (dd, $^{2,3}J_{\text{HH}}$ = 14.0, 7.0 Hz, COCHCH₂, 1H), 3.62 (dd, $^{2,3}J_{\text{HH}}$ = 14.0, 7.5 Hz, COCHCH₂, 1H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 168.6 (C=O), 167.6 (C=N), 155.9 (ArC), 148.7 (ArC), 147.1 (ArC), 145.9 (ArC), 141.9 (ArC), 138.9 (ArC), 136.8 (ArC), 131.4 (ArC), 130.8 (ArC), 129.9 (ArC x 2), 128.8 (ArC x 2), 128.3 (ArC x 2), 126.3 (ArC), 125.2 (ArC), 125.1 (ArC), 124.8 (ArC x 2), 124.4 (ArC x 2), 123.8 (ArC), 65.8 (COCHCH₂), 37.8 (COCHCH₂).

HRMS-ESI (m/z) calculated for $\text{C}_{27}\text{H}_{20}\text{N}_4\text{O}_3$ [$+\text{H}$]⁺: 449.1608, found: 449.1617. LCMS purity (UV) = 99 %, tR 20.81 min.

5.4.10 1-(4-Nitrophenyl)-3-benzyl-5-(2'-fluorobiphenyl-2-yl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.10**)

The product was obtained as white solid (0.03 mmol scale, 11 mg, 70%).

^1H -NMR (500 MHz) CDCl_3 : δ = 8.14 (d, $^3J_{\text{HH}}$ = 8.5 Hz, ArH, 2H), 7.57 – 7.52 (m, ArH, 1H), 7.51 – 7.45 (m, ArH, 1H), 7.42 (d, $^3J_{\text{HH}}$ = 7.5 Hz, ArH, 1H), 7.38 (d, $^3J_{\text{HH}}$ = 7.5 Hz, ArH, 1H), 7.32 – 7.27 (m, ArH, 7H), 7.26 – 7.19 (m, ArH, 2H), 7.15 – 7.09 (m, ArH, 1H), 7.06 (d, $^3J_{\text{HH}}$ = 7.5 Hz, ArH, 1H), 7.00 – 6.93 (m, ArH, 3H), 6.65 (d, $^3J_{\text{HH}}$ = 8.5 Hz, ArH, 1H), 3.80 (dd, $^3J_{\text{HH}}$ = 8.0, 5.5 Hz, COCHCH_2 , 1H), 3.69 (d, $^3J_{\text{HH}}$ = 8.0 Hz, COCHCH_2 , 1H), 3.66 (d, $^3J_{\text{HH}}$ = 8.0 Hz, COCHCH_2 , 1H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 169.5 (C=O), 167.9 (C=N), 159.2 (d, $^1J_{\text{FC}}$ = 247.5 Hz, ArC), 147.1 (ArC), 145.7 (ArC), 141.5 (ArC), 138.8 (ArC), 138.7 (ArC), 135.7 (ArC), 132.0 (d, $^3J_{\text{FC}}$ = 3.5 Hz, ArC), 131.6 (ArC), 131.4 (ArC), 130.8 (ArC), 130.3 (ArC), 129.9 (ArC x 2), 129.8 (ArC), 129.5 (ArC), 129.2 (ArC), 128.9 (d, $^3J_{\text{FC}}$ = 8.0 Hz, ArC), 128.5 (ArC x 2), 128.3 (ArC x 2), 128.1 (ArC), 126.3 (ArC), 125.2 (ArC), 124.8 (ArC), 124.5 (d, $^4J_{\text{FC}}$ = 3.5 Hz, ArC), 124.2 (ArC x 2), 115.4 (d, $^2J_{\text{FC}}$ = 22.0 Hz, ArC), 66.0 (COCHCH_2), 37.8 (COCHCH_2).

HRMS-ESI (m/z) calculated for $\text{C}_{34}\text{H}_{24}\text{N}_3\text{O}_3$ $[\text{+H}]^+$: 542.1874, found: 542.1881. LCMS purity (UV) = 93%, tR 23.27 min.

5.4.11 1-(2,4,6-Trimethylphenyl)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.13**)

The reaction was run for 8 hours. The product was obtained as white solid (1.00 mmol scale, 181 mg, 51%).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.60 – 7.57 (m, ArH, 2H), 7.54 – 7.46 (m, ArH, 4H), 7.32 (d, $^3J_{\text{HH}}$ = 8.0 Hz, ArH, 1H), 7.27 – 7.23 (m, ArH, 1H), 7.10 – 7.07 (m, ArH, 1H), 6.88 (s, ArH, 1H), 6.78 (d, $^3J_{\text{HH}}$ = 8.0, 1.1 Hz, ArH, 1H), 4.70 (d, $^2J_{\text{HH}}$ = 10.0 Hz, COCH_2 , 1H), 4.04 (d, $^2J_{\text{HH}}$ = 10.0 Hz, COCH_2 , 1H), 2.26 (s, CH_3 , 3H), 2.24 (s, CH_3 , 3H), 1.61 (s, CH_3 , 3H).

^{13}C -NMR (126 MHz) $\text{DMSO}-d_6$: δ = 170.3 (C=O), 167.5 (C=N), 142.2 (ArC), 138.9 (ArC), 137.9 (ArC), 137.0 (ArC), 136.2 (ArC), 134.7 (ArC), 132.3 (ArC), 130.9 (ArC), 130.0 (ArC x 2), 129.6 (ArC x 2), 129.5 (ArC), 128.9 (ArC x 2), 128.7 (ArC), 124.4 (ArC), 122.1 (ArC), 57.3 (COCH_2), 21.0 (CH_3), 18.5 (CH_3), 17.5 (CH_3).

HRMS-ESI (m/z) calculated for $C_{24}H_{22}N_2O$ $[+H]^+$: 355.1805, found: 355.1804. LCMS purity (UV) = 97%, tR 21.13 min.

5.4.12 1-(2-Bromophenyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**5.14**)

The reaction was run for 8 hours. The product was obtained as white solid (1.00 mmol scale, 31 mg, 8%).

1H NMR (500 MHz, DMSO- d_6) δ 7.84 (d, $^3J_{HH} = 8.0$ Hz, ArH, 1H), 7.70 (d, $^3J_{HH} = 8.0$ Hz, ArH, 1H), 7.66 – 7.59 (m, ArH, 4H), 7.52 – 7.46 (m, ArH, 3H), 7.41 – 7.37 (m, ArH, 1H), 7.32 (dd, $J = 7.8, 1.7$ Hz, ArH, 1H), 7.27 (d, $^3J_{HH} = 7.0$ Hz, ArH, 1H), 6.92 – 6.83 (m, ArH, 1H), 4.69 (d, $^2J_{HH} = 10.5$ Hz, COCH $_2$, 1H), 4.01 (d, $^2J_{HH} = 10.5$ Hz, COCH $_2$, 1H).

^{13}C -NMR (126 MHz) $CDCl_3$: δ = 170.7 (C=O), 168.9 (C=N), 142.0 (ArC), 138.9 (ArC), 138.6 (ArC), 134.3 (ArC), 133.7 (ArC), 132.0 (ArC), 131.0 (ArC), 130.9 (ArC), 130.8 (ArC), 129.9 (ArC x 2), 129.8 (ArC), 129.1 (ArC), 128.8 (ArC x 2), 124.7 (ArC), 123.0 (ArC), 121.5 (ArC), 57.0 (COCH $_2$).

HRMS-ESI (m/z) calculated for $C_{21}H_{15}BrN_2O$ $[+H]^+$: 391.0441, found: 391.0457. LCMS purity (UV) = 93%, tR 15.23 min.

5.4.13 1-(3'-Trifluoromethylphenyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**5.15**)

The reaction was run for 8 hours. The product was obtained as white solid (0.50 mmol scale, 80 mg, 42%).

1H -NMR (500 MHz) $CDCl_3$: δ = 7.72 (d, $^3J_{HH} = 7.5$ Hz, ArH, 2H), 7.60 – 7.55 (m, ArH, 2H), 7.53 (d, $^3J_{HH} = 8.5$ Hz, ArH, 2H), 7.49 – 7.45 (m, ArH, 2H), 7.44 – 7.38 (m, ArH, 3H), 7.25 – 7.20 (m, ArH, 1H), 6.92 (d, $^3J_{HH} = 8.5$ Hz, ArH, 1H), 4.95 (d, $^2J_{HH} = 10.5$ Hz, 1H), 4.02 (d, $^2J_{HH} = 10.5$ Hz, 1H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 170.3 (C=O), 168.3 (C=N), 143.1 (ArC), 141.3 (ArC), 138.6 (ArC), 132.0(q, $^2J_{\text{FC}}$ = 29.9 Hz, ArC), 131.9 (ArC), 131.6 (ArC), 131.4 (ArC), 130.7 (ArC), 130.4 (ArC), 129.8 (ArC x 2), 129.5 (ArC), 128.5 (ArC x 2), 125.2 (q, $^3J_{\text{FC}}$ = 3.5 Hz, ArC), 124.8(ArC), 124.8(ArC), 123.5 (q, $^1J_{\text{FC}}$ = 273.0 Hz, ArC), 124.2 (q, $^3J_{\text{FC}}$ = 3.5 Hz, ArC), 57.3 (COCH₂).

HRMS-ESI (m/z) calculated for $\text{C}_{22}\text{H}_{15}\text{F}_3\text{N}_2\text{O}$ [$+\text{H}$]⁺: 381.1209, found: 381.1208. LCMS purity (UV) = 96%, tR 21.35 min.

5.4.14 1-Phenyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.16**)

The reaction was run for 8 hours. The product was obtained as white solid (0.50 mmol scale, 14 mg, 9%).

^1H -NMR (500 MHz) CDCl_3 : δ = 7.72 (d, $^3J_{\text{HH}}$ = 7.5 Hz, ArH, 2H), 7.54 – 7.49 (m, ArH, 1H), 7.47 (d, $^3J_{\text{HH}}$ = 7.5 Hz, ArH, 2H), 7.43 – 7.38 (m, ArH, 2H), 7.37 – 7.30 (m, ArH, 2H), 7.24 – 7.21 (m, ArH, 3H), 7.20 – 7.16 (m, ArH, 1H), 6.97 (d, $^3J_{\text{HH}}$ = 8.5 Hz, ArH, 1H), 4.96 (d, $^2J_{\text{HH}}$ = 10.5 Hz, ArH, COCH₂, 1H), 4.01 (d, $^2J_{\text{HH}}$ = 10.5 Hz, COCH₂, 1H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 170.7 (C=O), 168.3 (C=N), 146.5 (ArC), 143.3 (ArC), 140.7 (ArC), 138.6 (ArC), 131.3 (ArC), 130.7 (ArC), 130.3 (ArC), 129.6 (ArC x 2), 129.3 (ArC x 2), 128.4 (ArC x 2), 128.3 (ArC x 2), 127.5 (ArC), 124.7 (ArC), 124.2 (ArC), 57.2 (COCH₂).

HRMS-ESI (m/z) calculated for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$ [$+\text{H}$]⁺: 313.1335, found: 313.1338. LCMS purity (UV) = 90%, tR 16.10 min.

5.4.15 1-(4-Nitrophenyl)-3-(4-nitrophenyl)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**5.18**)

The product was obtained as white solid (0.60 mmol scale, 2 eq. of diaryliodonium triflate, 146 mg, 51%).

^1H -NMR (500 MHz) CDCl_3 : δ = 8.34 – 8.22 (m, ArH, 4H), 7.85 – 7.79 (m, ArH, 2H), 7.77 – 7.71 (m, ArH, 2H), 7.74 – 7.57 (m, ArH, 3H), 7.59 – 7.50 (m, ArH, 3H), 7.41 – 7.32 (m, ArH, 2H), 7.07 – 7.02 (m, ArH, 1H).

^{13}C -NMR (126 MHz) CDCl_3 : δ = 166.0 (C=O), 158.3 (C=N), 149.1 (ArC), 146.7 (ArC), 145.6 (ArC), 144.1 (ArC), 143.3 (ArC), 135.0 (ArC), 132.6 (ArC), 131.5 (ArC), 129.9 (ArC), 129.6 (ArC), 129.5 (ArC x 2), 128.9 (ArC x 2), 126.8 (ArC x 2), 126.3 (ArC), 125.4 (ArC), 124.5 (ArC x 2), 124.3 (ArC x 2), 121.3 (ArC x 2).

HRMS-ESI (m/z) calculated for $\text{C}_{26}\text{H}_{17}\text{N}_5\text{O}_5$ [$+\text{H}$] $^+$: 480.1230 found: 480.1245. LCMS purity (UV) = 95%, tR 18.35 min.

5.4.16 1,1'-Oxybis(4-nitrobenzene) (**5.21**)

To a solution of (4-nitrophenyl)phenyliodonium triflate (30 mg, 0.06 mmol) in DCE (1 mL) was added sodium hydroxide (aq., 1 mL) and stirred for 20 min. at room temperature. Upon completion, the reaction was diluted with dichloromethane (5 mL x 3) and the layers were separated. Combined organic layers were dried (MgSO_4) and concentrated under reduced pressure to afford the product as a white powder (7 mg, 43%).

^1H -NMR (500 MHz) CDCl_3 : δ = 8.33 – 8.27 (m, ArH, 4H), 7.19 – 7.14 (m, ArH, 4H). ^{13}C -NMR (126 MHz) CDCl_3 : δ = 160.6 (ArC x 2), 144.2 (ArC x 2), 126.2 (ArC x 4), 119.3 (ArC x 4).

HRMS-ESI (m/z) calculated for $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_5$ [$+\text{H}$] $^+$: 261.0511, found: 261.0513.

5.5 References

- 1 P. Filippakopoulos, J. Qi, S. Picaud, Y. Shen, W. B. Smith, O. Fedorov, E. M. Morse, T. Keates, T. T. Hickman, I. Felletar, M. Philpott, S. Munro, M. R. McKeown, Y. Wang, A. L. Christie, N. West, M. J. Cameron, B. Schwartz, T. D. Heightman, N. La Thangue, C. A. French, O. Wiest, A. L. Kung, S. Knapp and J. E. Bradner, *Nature*, 2010, **468**, 1067–1073.

- 2 G. F. Field, W. J. Zally and L. H. Sternbach, *J. Am. Chem. Soc.*, 1967, **39****57**, 332–338.
- 3 J. A. Ellman, *Acc. Chem. Res.*, 1996, **29**, 132–143.
- 4 A. Nadin, M. Sa, A. P. Owens, D. M. Howells, A. C. Talbot and T. Harrison, *J. Org. Chem.*, 2003, **2**, 2844–2852.
- 5 M. G. J. Baud, E. Lin-shiao, T. Cardote, C. Tallant, A. Pschibul, K. Chan, M. Zengerle, J. R. Garcia, K. Terence, F. M. Ferguson and A. Ciulli, *Science.*, 2014, **346**, 638–641.
- 6 M. G. J. Baud, E. Lin-Shiao, M. Zengerle, C. Tallant and A. Ciulli, *J. Med. Chem.*, 2016, **59**, 1492–1500.
- 7 O. Mirguet, R. Gosmini, J. Toum, C. A. Clément, M. Barnathan, J. M. Brusq, J. E. Mordaunt, R. M. Grimes, M. Crowe, O. Pineau, M. Ajakane, A. Daugan, P. Jeffrey, L. Cutler, A. C. Haynes, N. N. Smithers, C. W. Chung, P. Bamborough, I. J. Uings, A. Lewis, J. Witherington, N. Parr, R. K. Prinjha and E. Nicodème, *J. Med. Chem.*, 2013, **56**, 7501–7515.
- 8 J. J. Liu, B. Higgins, G. Ju, K. Kolinsky, K. C. Luk, K. Packman, G. Pizzolato, Y. Ren, K. Thakkar, C. Tovar, Z. Zhang and P. M. Wovkulich, *ACS Med. Chem. Lett.*, 2013, **4**, 259–263.
- 9 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfieldt, *J. Med. Chem.*, 1988, **31**, 2235–2246.
- 10 P. Filippakopoulos, S. Picaud, O. Fedorov, M. Keller, M. Wrobel, O. Morgenstern, F. Bracher and S. Knapp, *Bioorganic Med. Chem.*, 2012, **20**, 1878–1886.
- 11 S. G. Smith, R. Sanchez and M. M. Zhou, *Chem. Biol.*, 2014, **21**, 573–583.
- 12 P. Filippakopoulos and S. Knapp, *Nat. Rev. Drug Discov.*, 2014, **13**, 337–356.
- 13 M. C. Carter, D. G. Alber, R. C. Baxter, S. K. Bithell, J. Budworth, A. Chubb, G. S. Cockerill, V. C. L. Dowdell, E. A. Henderson, S. J. Keegan, R. D. Kelsey, M. J. Lockyer, J. N. Stables, L. J. Wilson and K. L. Powell, *J. Med. Chem.*, 2006, **49**, 2311–2319.
- 14 S. M. Ghelani and Y. T. Naliapara, *J. Heterocycl. Chem.*, 2016, **53**, 1843–1851.
- 15 H. Abdelkafi and J.-C. Cintrat, *Sci. Rep.*, 2015, **5**, 12131.
- 16 N. Kaur, *Int. J. Pharma Bio Sci.*, 2013, **4**, 485–513.
- 17 X. Hu, Y. Dong and G. Liu, *Mol. Divers.*, 2015, **19**, 695–701.

- 18 J. Spencer, R. P. Rathnam and B. Z. Chowdhry, *Future Med. Chem.*, 2010, **2**, 1441–1449.
- 19 E. K. Dziadulewicz, M. C. Brown, A. R. Dunstan, W. Lee, N. B. Said and P. J. Garratt, *Bioorganic Med. Chem. Lett.*, 1999, **9**, 463–468.
- 20 I. M. McDonald, C. Austin, I. M. Buck, D. J. Dunstone, J. Gaffen, E. Griffin, E. a. Harper, R. a D. Hull, S. B. Kalindjian, I. D. Linney, C. M. R. Low, D. Patel, M. J. Pether, M. Raynor, S. P. Roberts, M. E. Shaxted, J. Spencer, K. I. M. Steel, D. a. Sykes, P. T. Wright and W. Xun, *J. Med. Chem.*, 2007, **50**, 4789–4792.
- 21 Guylaine Cuny, and Michèle Bois-Choussy and J. Zhu, *J. Am. Chem. Soc.*, 2004, **34**, 14475–14484.
- 22 A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald and R. V May, *J. Am. Chem. Soc.*, 2001, **123**, 7727–7729.
- 23 D. Talukdar, G. Das, S. Thakur, N. Karak and A. J. Thakur, *Catal. Commun.*, 2015, **59**, 238–243.
- 24 S. M. Strittmatter, *Nat. Med.*, 2014, **20**, 590–591.
- 25 S. M. Corsello, J. A. Bittker, Z. Liu, J. Gould, P. McCarren, J. E. Hirschman, S. E. Johnston, A. Vrcic, B. Wong, M. Khan, J. Asiedu, R. Narayan, C. C. Mader, A. Subramanian and T. R. Golub, *Nat. Med.*, 2017, **23**, 405–408.
- 26 J. Spencer, R. P. Rathnam, A. L. Harvey, C. J. Clements, R. L. Clark, M. P. Barrett, P. E. Wong, L. Male, S. J. Coles and S. P. MacKay, *Bioorganic Med. Chem.*, 2011, **19**, 1802–1815.
- 27 R. L. Clark, C. J. Clements, M. P. Barrett, S. P. MacKay, R. P. Rathnam, G. Owusu-Dapaah, J. Spencer and J. K. Huggan, *Bioorganic Med. Chem.*, 2012, **20**, 6019–6033.
- 28 J. Spencer, B. Z. Chowdhry, A. I. Mallet, R. P. Rathnam, T. Adatia, A. Bashall and F. Rominger, *Tetrahedron*, 2008, **64**, 6082–6089.
- 29 R. Khan, R. Felix, P. D. Kemmitt, S. J. Coles, I. J. Day, G. J. Tizzard and J. Spencer, *Adv. Synth. Catal.*, 2016, **358**, 98–109.
- 30 E. A. Merritt and B. Olofsson, *Angew. Chemie - Int. Ed.*, 2009, **48**, 9052–9070.
- 31 M. Bielawski, D. Aili and B. Olofsson, *J. Org. Chem.*, 2008, **73**, 4602–4607.
- 32 M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, *Arkivoc*, 2011, **2011**, 370–409.
- 33 L. Marzo, I. Ghosh, F. Esteban and B. König, *ACS Catal.*, 2016, **6**, 6780–6784.
- 34 F. Tinnis, E. Stridfeldt, H. Lundberg, H. Adolfsson and B. Olofsson, *Org. Lett.*,

- 2015, **17**, 2688–2691.
- 35 J. Malmgren, S. Santoro, N. Jalalian, F. Himo and B. Olofsson, *Chem. - A Eur. J.*, 2013, **19**, 10334–10342.
- 36 Z. Gonda and Z. Novák, *Chem. Eur. J.*, 2015, **21**, 16801–16806.
- 37 M. Lanning and S. Fletcher, *Futur. Med. Chem.*, 2013, **5**, 2157–2174.
- 38 V. Azzarito, K. Long, N. S. Murphy and A. J. Wilson, *Nat. Chem.*, 2013, **5**, 161–173.
- 39 E. Stridfeldt, E. Lindstedt, M. Reitti, J. Blid, P. O. Norrby and B. Olofsson, *Chem. - A Eur. J.*, 2017, **23**, 13249–13258.
- 40 S. J. Coles and P. A. Gale, *Chem. Sci.*, 2012, **3**, 683–689.

Chapter 6

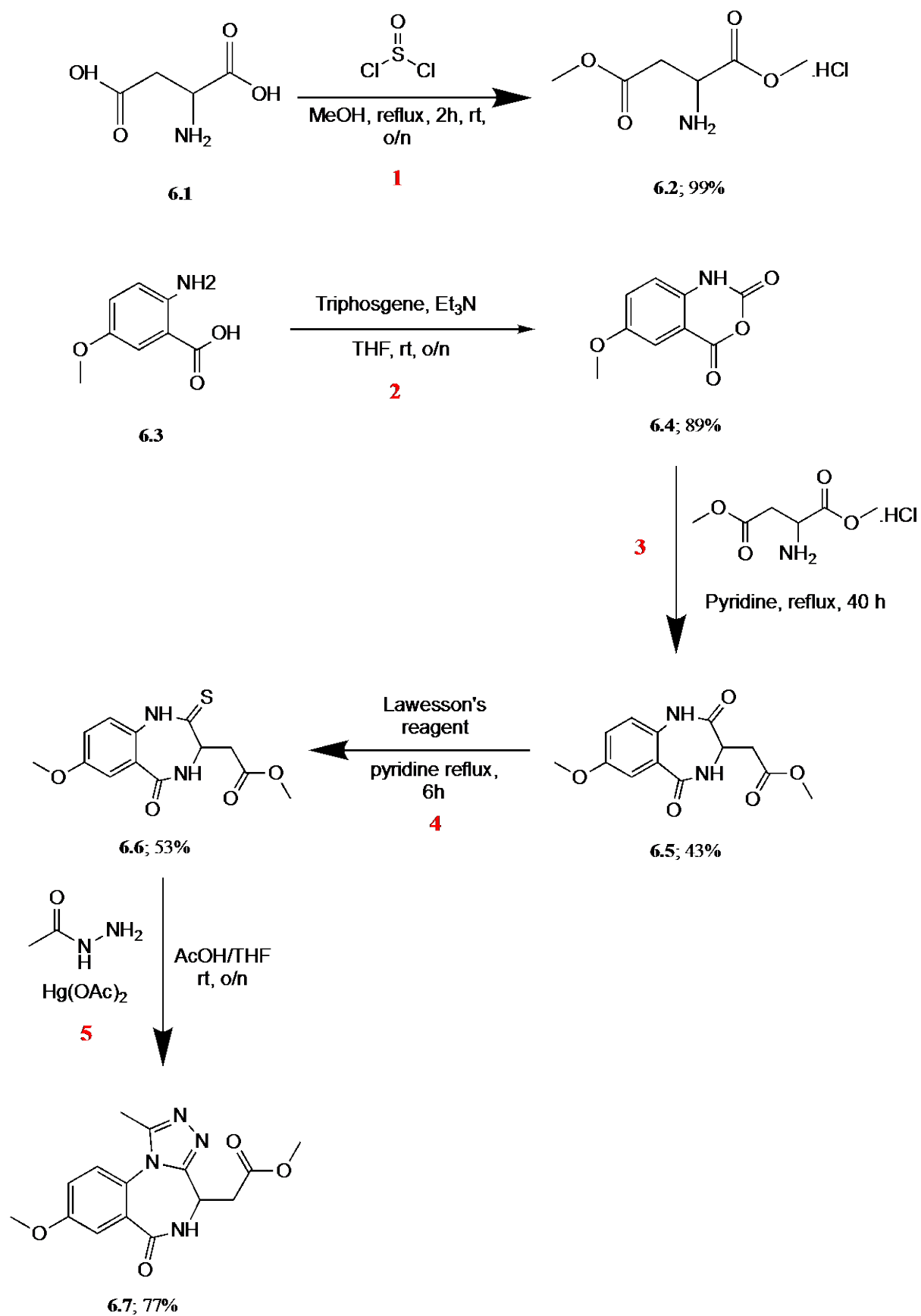
Gram Scale Laboratory Synthesis of TC AC 28, a High Affinity BET Bromodomain Ligand

6.1 Introduction

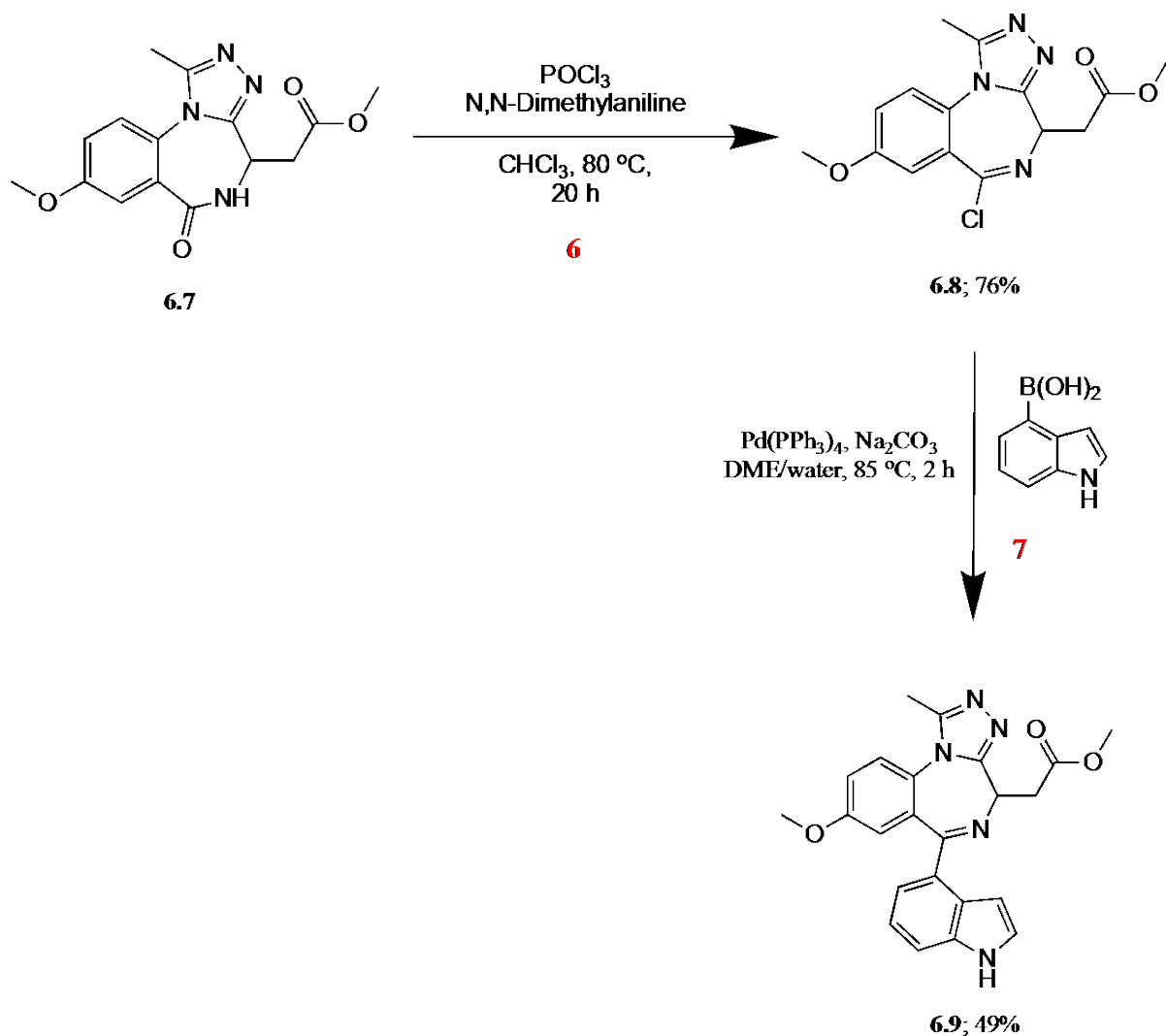
The 1,4-benzodiazepine scaffold is a well-established “privileged scaffold” in medicinal chemistry^{1–17} and as stated in the previous Chapters, we have an active interest in synthesising libraries of such compounds.^{18–22} Triazolo-benzodiazepine derivative **TC AC 28** is a potent, selective BET (Bromo and extraterminal) bromodomain inhibitor and a useful epigenetic tool compound.^{23,24} We sought to scale up the original seven-step-protocol towards this molecule with the aim of improving the final two problematic and low yielding steps.²

6.2 Results and Discussion

Our scale-up efforts (step 1, Scheme 6.1) started with a synthesis of the methyl ester hydrochloride salt **6.2**, which was formed in virtually quantitative yield, followed a cyclization step (step 2) to afford the isatoic anhydride **6.4**.²⁵

Scheme 6.1: Synthesis of triazolo-benzadiazepinone, **6.7**

Reaction of the latter, formed the benzodiazepinedione **6.5**, and we employed an ether trituration, as opposed to our earlier reported chromatographic purification work-up. This was followed by treatment with Lawesson's reagent,^{26,27} by mercury-mediated cyclization to afford the triazolo-analogue **6.7** (steps 3 – 5). At this stage, no significant differences in yields were noticed from our original report. However, the next two crucial steps were vital in our aims to obtain approximate gram quantities of product.



Scheme 6.2: Synthesis of **TC AC 28 (6.9)**

Step 6 (Scheme 6.2) was originally performed by combining 12 batches of *ca.* 170 mg amounts of precursor **6.7**, yielding the key chloroimidate intermediate **6.8**, which was obtained as a white solid in 619 mg amounts (29% yield). Careful re-examination of this step led us to significantly lower the amounts of POCl₃ used and we were able to avoid the inefficient chromatographic step by carrying out a trituration in Et₂O (Table 6.1, Entry 3). Indeed, we were delighted to obtain a yield of 76% of **6.8** in nearly gram quantities (0.80 g) in a one-step protocol.

Table 6.1: Step 6 optimisation

Entry	POCl ₃ (eq.)	N,N-DMA (eq.)	Work up	Purification	Isolated Yield (8) (%)
1	21	5.5	Quench (Et ₃ N)	Acetone/DCM (30% to 80%) column	20 ^a
2	10	3	Quench (water) extraction with CHCl ₃	Trituration with diethyl ether.	50
3	1.5	2	Quench (water) extraction with CHCl ₃	Trituration with diethyl ether.	76

^aMaterial decomposes in silica

Buoyed by this result we next examined the final Pd-catalyzed Suzuki-Miyaura coupling reaction in order to install the indolyl group in **6.9**.^{28,29} Maintaining the original Pd(PPh₃)₄ catalyst, we obtained, by using a DME/water mixture with Na₂CO₃ as base, **6.9** in 49% yield (Table 3, Entry 2), which was scalable to 0.8 g of product (Table 2).

Table 6.2: Suzuki Coupling Optimization

Entry	Catalyst	Solvent	Base	Conditions	Isolated Yield (9) (%)
1	Pd(PPh ₃) ₄	DMF	Et ₃ N	100 °C, 24 h	27
2	Pd(PPh ₃) ₄	DME/ Water	Na ₂ CO ₃	85 °C, 2 h	49

Table 6.3: Comparison of scale-up vs. original published route

Step	S.M. (g) ^a	Prod. (g)	yield(%)	S.M. (g) ^b	Prod.(g)	yield (%)
1	50.07	74.00	>99	-	-	-
2	50.02	57.03	89	-	-	>99
3	45.00	27.30	43 ^c	3.70	1.77	36
4	15.01	8.30	53	1.86	1.12	57
5	8.00	6.57	77 ^d	2.20	2.15	91
6	0.99	0.80	76 ^e	2.04 (0.17 x 12)	0.619	29
7	1.33	0.81	49	-	-	27-31

^aScale up; S.M. =starting material, Prod.= product. ^bOriginal papers. ^cTrituration in ether as opposed to chromatography. ^dReaction mixture quenched with NaHCO₃ extracted with ethyl acetate as opposed to no work-up. ^ePOCl₃ (1.5 eq), DMA (2 eq.) quenched with water, extraction with CHCl₃ and trituration with diethyl ether as opposed to POCl₃ (21 eq). DMA (5.5 eq.), quenched with Et₃N and purified by chromatography. ^ePd(PPh₃)₄, DME/water and Na₂CO₃ as opposed to Pd(PPh₃)₄, DMF and Et₃N.

6.3 Conclusion

Overall, acceptable, near gram quantities of the final product **6.9** have been synthesized, benefitting ultimately from improved steps 6 and 7 of the original synthetic route (Table 6.3).

6.4 Experimental details for Chapter 6

All commercially purchased materials and solvents were used without further purification unless specified otherwise. NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer and prepared in deuterated solvents such as CDCl₃ and DMSO-d₆. LC-MS spectra were acquired using an Agilent 6120 (600 Bar) HPLC with Agilent 1290 MCT column compartment oven and Agilent 6120 Quad Mass Spectrometer and percentage purities were run on a Zorbax SB C18 2.1x 50 mm 1.8 μm column (0.1% aq. Formic Acid 0.1% Formic Acid in MeCN 5-95%, 0.1% TFA/MeCN, over 5 min, held at 100 % for 2 min, flow rate – 0.5mL/min) with the UV detector at 250 nm, bandwidth 100 nm. Purifications were performed by flash chromatography on silica gel columns using a Reveleris PREP purification system.

6.4.1 (DL)-Aspartic acid dimethyl ester hydrochloride (**6.2**)

To a suspension of DL-Aspartic acid (50.00 g, 375.65 mmol) in methanol (300 mL) at 0 °C was dropwise added thionyl chloride (68.50 mL, 939.14 mmol, 2.5 eq.) at such a rate that the temperature was maintained below 10 °C. Upon completion of the addition, the reaction mixture was stirred at reflux for 2 hours, and then allowed to cool to ambient temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure and the resulting viscous oil was triturated from diethyl ether, filtered and dried at 40 °C under vacuum, affording the product as a white solid (74.00 g, > 99%). The spectral data were consistent with those reported.³⁰

6.4.2 5-Methoxyisatoic anhydride (**6.4**)

To a stirred solution of 2-amino-5-methoxy-benzoic acid **6.3** (15.00 g, 99.23 mmol) and triethylamine (13.80 mL, 99.23 mmol, 1 eq.) in THF (500 mL) at 0 °C was portion-wise added triphosgene (29.45 g, 99.23 mmol, 1 eq.) at such a rate that the temperature was maintained below 5 °C. Upon completion of the addition, the reaction mixture was stirred for 18 hours at ambient temperature. The reaction was re-cooled to 0 °C and H₂O (15 mL) was added in a dropwise fashion at such a rate that the temperature was maintained below 10 °C. After stirring for further 30 min at ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was triturated with H₂O and the resulting solid was collected by filtration and dried at 50 °C under vacuum, affording the product as a brown solid (17.00 g, 89%). LCMS purity (UV): 99%, t_R 3.24 min. The NMR data were consistent with those reported.²⁴

6.4.3 Methyl-2-(7-methoxy-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepin-3-yl)acetate (**6.5**)

5-Methoxyisatoic anhydride **6.4** (45.00 g, 232.97 mmol) and DL-aspartic acid dimethyl ester hydrochloride (46.04 g, 232.99 mmol, 1 eq.) were suspended in pyridine (600 mL) and the reaction mixture was stirred at reflux for 18 hours. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (500 mL) and 2 M HCl (500 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (2 x 350 mL). Some solid material at the phase boundary was collected by filtration giving an initial crop of product. The combined organic phase of the filtrate was dried (MgSO₄) and concentrated under reduced pressure. Trituration with diethyl ether afforded the product as a white solid (27.30 g, 43%). LCMS purity (UV): 96%, t_R 3.12 min. The NMR data were consistent with those reported.²⁴

6.4.4 (+)-Methyl-2-(7-methoxy-5-oxo-2-thioxo-2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepin-3-yl)acetate (**6.6**)

To a suspension of the previous compound **6.5** (15.01 g, 53.91 mmol) in pyridine (265 mL) was added Lawesson's reagent (19.62 g, 48.52 mmol, 0.9 eq.) and the reaction mixture was stirred at reflux for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was suspended in

CH₂Cl₂ (3 x 300 mL) and re-concentrated under reduced pressure. Trituration with CH₂Cl₂ afforded the product as a pale yellow solid (8.30 g, 53%). LCMS purity (UV): 92%, tR 3.51 min. The NMR data were consistent with those reported.²⁴

6.4.5 (+-)-Methyl-2-(8-methoxy-1-methyl-6-oxo-5,6-dihydro-4*H*-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetate (**6.7**)

To a stirred suspension of compound **6.6** (8.00 g, 27.18 mmol) and acethydrazide (6.04 g, 81.53 mmol, 3 eq.) in THF (120 mL) was added acetic acid (80 mL). The reaction mixture was cooled to 0°C and mercury (II) acetate (12.91 g, 40.77 mmol, 1.5 eq.) was added to the reaction mixture portion-wise at such a rate that the temperature was maintained below 5°C. Upon completion of the addition, the reaction mixture was stirred at 0°C for 2 hours, and then allowed to warm to ambient temperature and stirred for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between NaHCO₃ (sat. aq., 450 mL) and ethyl acetate (300 mL). The aqueous component was separated and extracted with ethyl acetate (2 x 300 mL). The combined organic layer was dried (MgSO₄) and concentrated under reduced pressure. The product was collected as a white solid (6.57 g, 77%) after flash column chromatography (95:5 CH₂Cl₂/MeOH). LCMS purity (UV): 95%, tR 3.15 min. The NMR data were consistent with those reported.²⁴

6.4.6 (+-)-Methyl-2-(6-chloro-8-methoxy-1-methyl-4*H*-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetate (**6.8**)

To a solution of compound **6.7** (0.99 g, 3.13 mmol) in CHCl₃ (20 mL) was added N,N-dimethylaniline (0.79 g, 6.26 mmol) and POCl₃ (0.72 g, 4.70 mmol) under inert atm. and the reaction was heated at 80°C for 18 hours. After cooling to room temperature, the reaction was slowly poured into lukewarm water (80 mL) with stirring. After stirring for 15 min, it was diluted with CHCl₃ (50 mL) and the layers were separated. The aqueous layer was extracted with further CHCl₃ (50 mL). The combined organic layer was dried (MgSO₄) and concentrated under reduced pressure. The residue was triturated with diethyl ether and to afford an off-white solid (0.80g, 76 %). The product was used without further purification. LCMS purity (UV): 97%, tR 3.94 min. The NMR data were consistent with those reported.²⁴

6.4.7 (+)-Methyl-2-(6-chloro-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetate (**6.9**)

To a stirred suspension of compound **6.8** (1.33 g, 3.97 mmol) in DME (14 mL) was added a solution of Na₂CO₃ (0.76 g, 7.17 mmol) in water (6 mL), followed by the addition of indole-4-boronic acid (0.77 g, 4.76 mmol) and Pd(PPh₃)₄ (0.31 g, 0.27 mmol) the reaction was heated at 85 °C for 2.5 hours. After cooling to ambient temperature, it was filtered over celite and the filtrate was partitioned between EtOAc/water. The layers were separated and the organic layer was further washed with water and brine. The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The product was collected as a white solid (0.81 g, 49%) after flash column chromatography (rf = 0.35; 95:5 CH₂Cl₂/MeOH).

¹H-NMR (400 MHz) CDCl₃: δ = 8.40 (s, 1H), 7.52 (d, *J* = 8.0, 1H), 7.42 (d, *J* = 9.0, 1H), 7.24 (t, *J* = 3.0, 1H), 7.20 (dd, *J* = 3.0, *J* = 9.0, 1H), 7.15 (t, *J* = 7.5, 1H), 7.08 (d, *J* = 7.5, 1H), 6.92 (d, *J* = 3.0, 1H), 6.58 (s, 1H), 4.78 (dd, *J* = 5.5, *J* = 9.0, 1H), 3.81 (s, 3H), 3.72 – 3.78 (m, 4H), 3.63 (dd, *J* = 5.5, *J* = 16.5, 1H), 2.64 (s, 3H).

LCMS purity (UV): 99%, tR 4.12 min. Elemental Analysis: Calculated for C₂₃H₂₁N₅O₃·^{3/4}H₂O (%): C, 64.4, H, 5.29, N, 16.33, found: C, 64.73, H, 5.12, N, 16.07. MS m/z (ES+) calculated for C₂₃H₂₁N₅O₃ [+H]⁺: 416.3 found: 416.3; m/z (ES-) calculated for C₂₃H₂₁N₅O₃ [-H]⁺: 414.3 found: 414.3.

6.5 References

- 1 J. A. Ellman, *Acc. Chem. Res.*, 1996, **29**, 132–143.
- 2 C.-W. Chung, H. Coste, J. H. White, O. Mirguet, J. Wilde, R. L. Gosmini, C. Delves, S. M. Magny, R. Woodward, S. A. Hughes, E. V Boursier, H. Flynn, A. M. Bouillot, P. Bamborough, J.-M. G. Brusq, F. J. Gellibert, E. J. Jones, A. M. Riou, P. Homes, S. L. Martin, I. J. Uings, J. Toum, C. a Clement, A. B. Boullay, R. L. Grimley, F. M. Blandel, R. K. Prinjha, K. Lee, J. Kirilovsky and E. Nicodeme, *J. Med. Chem.*, 2011, **54**, 3827–3838.
- 3 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D.

- J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfieldt, *J. Med. Chem.*, 1988, **31**, 2235–2246.
- 4 S. G. Smith, R. Sanchez and M. M. Zhou, *Chem. Biol.*, 2014, **21**, 573–583.
 - 5 S. G. Smith and M. M. Zhou, *ACS Chem. Biol.*, 2016, **11**, 598–608.
 - 6 E. Nicodeme, K. L. Jeffrey, U. Schaefer, S. Beinke, S. Dewell, C. Chung, R. Chandwani, I. Marazzi, P. Wilson, H. Coste, J. White, J. Kirilovsky, C. M. Rice, J. M. Lora, R. K. Prinjha, K. Lee and A. Tarakhovsky, *Nature*, 2010, **468**, 1119–1123.
 - 7 P. Filippakopoulos, S. Picaud, O. Fedorov, M. Keller, M. Wrobel, O. Morgenstern, F. Bracher and S. Knapp, *Bioorganic Med. Chem.*, 2012, **20**, 1878–1886.
 - 8 P. Filippakopoulos and S. Knapp, *Nat. Rev. Drug Discov.*, 2014, **13**, 337–356.
 - 9 H. Abdelkafi and J.-C. Cintrat, *Sci. Rep.*, 2015, **5**, 12131.
 - 10 E. Section, G. F. Field and L. H. Sternbach, 1967, **3957**, 332–338.
 - 11 E. K. Dziadulewicz, M. C. Brown, A. R. Dunstan, W. Lee, N. B. Said and P. J. Garratt, *Bioorganic Med. Chem. Lett.*, 1999, **9**, 463–468.
 - 12 L. Guandalini, C. Cellai, A. Laurenzana, S. Scapecchi, F. Paoletti and M. N. Romanelli, *Bioorganic Med. Chem. Lett.*, 2008, **18**, 5071–5074.
 - 13 S. M. Ghelani and Y. T. Naliapara, *J. Heterocycl. Chem.*, 2016, **53**, 1843–1851.
 - 14 A. El Bouakher, G. Prié, M. Aadil, M. Akssira and M. C. Viaud-Massuard, *Tetrahedron*, 2013, **69**, 5086–5091.
 - 15 N. Kaur, *Int. J. Pharma Bio Sci.*, 2013, **4**, 485–513.
 - 16 X. Hu, Y. Dong and G. Liu, *Mol. Divers.*, 2015, **19**, 695–701.
 - 17 A. M. Taylor, R. G. Vaswani, V. S. Gehling, M. C. Hewitt, Y. Leblanc, J. E. Audia, S. Bellon, R. T. Cummings, A. Côté, J.-C. Harmange, H. Jayaram, S. Joshi, J. M. Lora, J. A. Mertz, A. Neiss, E. Pardo, C. G. Nasveschuk, F. Poy, P. Sandy, J. W. Setser, R. J. Sims, Y. Tang and B. K. Albrecht, *ACS Med. Chem. Lett.*, 2016, **7**, 145–150.
 - 18 J. Spencer, B. Z. Chowdhry, A. I. Mallet, R. P. Rathnam, T. Adatia, A. Bashall and F. Rominger, *Tetrahedron*, 2008, **64**, 6082–6089.
 - 19 J. Spencer, R. P. Rathnam and B. Z. Chowdhry, *Future Med. Chem.*, 2010, **2**, 1441–1449.
 - 20 J. Spencer, R. P. Rathnam, A. L. Harvey, C. J. Clements, R. L. Clark, M. P. Barrett, P. E. Wong, L. Male, S. J. Coles and S. P. MacKay, *Bioorganic Med. Chem.*, 2011, **19**, 1802–1815.

- 21 R. L. Clark, C. J. Clements, M. P. Barrett, S. P. MacKay, R. P. Rathnam, G. Owusu-Dapaah, J. Spencer and J. K. Huggan, *Bioorganic Med. Chem.*, 2012, **20**, 6019–6033.
- 22 R. Khan, R. Felix, P. D. Kemmitt, S. J. Coles, I. J. Day, G. J. Tizzard and J. Spencer, *Adv. Synth. Catal.*, 2016, **358**, 98–109.
- 23 M. G. J. Baud, E. Lin-shiao, T. Cardote, C. Tallant, A. Pschibul, K. Chan, M. Zengerle, J. R. Garcia, K. Terence, F. M. Ferguson and A. Ciulli, *Science (80-.)*, 2014, **346**, 638–641.
- 24 M. G. J. Baud, E. Lin-Shiao, M. Zengerle, C. Tallant and A. Ciulli, *J. Med. Chem.*, 2016, **59**, 1492–1500.
- 25 M. C. Carter, D. G. Alber, R. C. Baxter, S. K. Bithell, J. Budworth, A. Chubb, G. S. Cockerill, V. C. L. Dowdell, E. A. Henderson, S. J. Keegan, R. D. Kelsey, M. J. Lockyer, J. N. Stables, L. J. Wilson and K. L. Powell, *J. Med. Chem.*, 2006, **49**, 2311–2319.
- 26 Y. Hitotsuyanagi, S. Motegi, H. Fukaya and K. Takeya, *J. Org. Chem.*, 2002, **67**, 3266–3271.
- 27 S. S. Syeda, S. Jakkaraj and G. I. Georg, *Tetrahedron Lett.*, 2015, **56**, 3454–3457.
- 28 A. Nadin, M. Sa, A. P. Owens, D. M. Howells, A. C. Talbot and T. Harrison, *J. Org. Chem.*, 2003, **2**, 2844–2852.
- 29 A. Boitano, J. A. Ellman, G. D. Glick and A. W. Opiari, *Cancer. Res.*, 2003, **63**, 6870–6876.
- 30 L. S. Fowler, D. Ellis and A. Sutherland, *Org. Biomol. Chem.*, 2009, **7**, 4309.

Chapter 7

7.1 Conclusions and Future Directions

Despite the commercial availability and well-developed synthetic routes for 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one skeletons, there is lack of atom economical late-stage functionalisation protocols for closely related BZD-based analogues. Therefore, this thesis aimed to develop efficient and atom economical routes for generating a BZD-based library. The ability to add functionality to bioactive cores and privileged scaffolds such as BZDs, at the final or penultimate synthetic step is very useful in medicinal chemistry and drug discovery to enable SAR studies that can drive efficiency and speed up hit-to-lead and lead optimization strategies.

In summary, this project aimed to synthesise libraries of functionalised 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives as shown in Figure 7.1, using efficient, one-step, atom-economical protocols.

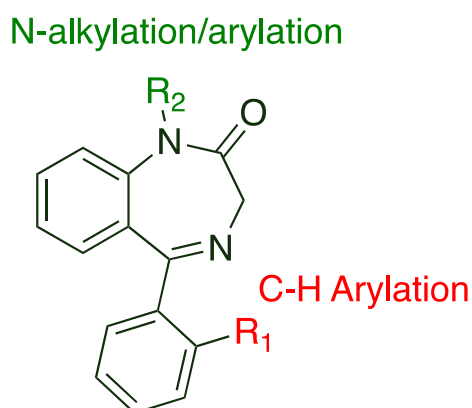


Figure 7. 27: Functionalisation scopes of BZD scaffold for library generation

Traditional approaches to introduce different R_1 groups require their introduction early in the synthetic sequence, which is often followed by repetitive coupling and cyclisation steps. Chapter 2, therefore, sought to functionalise at the ortho-position by introducing various R_1 groups via a late-stage C-H activation. Atom and step economy in library generation could be achieved by synthesising the BZD scaffold in large scale and adding the new functional groups at the final step. Moreover, microwave mediated chemistry was employed for quicker and further efficiency in the generation of a library of ortho-arylated 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one. A series of over twenty novel BZD analogues were synthesised employing the microwave mediated Pd catalysed C-H arylation protocol with diaryliodonium tetrafluoroborates. The methodology is also applicable to nordazepam, the active metabolite of diazepam. The compounds were further diversified by N-alkylation and H/D exchange, which produces functionalised pharmaceuticals (e.g. ortho-arylated diazepam and pinazepam).

Considering the relatively high commercial cost and multistep synthesis of diaryliodonium salts, as well as the loss of an aryl iodide, lowering the atom economy of these processes, this project next explored a visible-light photocatalyzed Pd-mediated protocol involving aryldiazonium salts. In this procedure, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones reacted with aryldiazonium salts under palladium and visible light photoredox catalysis in refluxing methanol. This protocol generally affords higher yields for generating libraries of ortho-arylated BZDs than our previous C-H method with diaryliodonium salts. Surprisingly, reactions with 2- and 4-fluorobenzenediazonium salts led to the methoxyaryl derivative in addition to the expected fluoroaryl products. The formation of the ether product can be explained by a competing S_NAr reaction, termed ‘nuisance effect’. The strong electron withdrawing effect of the diazo group gives rise to this effect for halogen substituted benzenediazonium salts, which is observed for 2- and 4-substituted isomers. Biological tests against GABA_A receptors revealed that the ortho-arylated were significantly less active than e.g. nordazepam and diazepam. A computational DFT study of the Pd-catalysed and the Pd/Ru photocatalysed mechanism for the functionalisation of benzodiazepines conducted by our collaborators indicated that in the presence of the photocatalyst, the reaction proceeds via a low-energy SET pathway and avoids the high-energy oxidative addition step in the palladium-only catalysed reaction pathway.

To extend the arylation/nuisance effect chemistry to a wider range of privileged structures, this chemistry was applied with substrates such as 1-phenyl-2-pyrrolidones and 2-phenylpyridines for library generation. Small arrays of fluoroaryl, methoxyaryl, ethoxyaryl and 2-propoxyaryl derivatives of 1-phenyl-2-pyrrolidones were synthesised using methanol, ethanol and 2-propanol as the solvent. The ratio of the ether product formation can be influenced by the reaction sequence (i.e., the ether product formation increases when the diazonium salt is refluxed before adding the substrate and the catalysts). Pleasantly, a one-pot reaction with separate alcohols led to small array ether products in addition to the expected fluoroaryl derivative of 1-phenyl-2-pyrrolidone. Moreover, a reaction of 2-phenylpyridine employing the arylation/nuisance effect chemistry led to five separable products from a combination of mono, di-arylation and “nuisance effects”. Biological tests performed by our collaborators revealed that a number of the ortho-arylated 1-phenyl-2-pyrrolidones bound to the protein NUDT7 α and produced X-ray co-crystals.

Continuing on the late-stage functionalisation of BZD scaffolds, in Chapter 5, we sought to synthesise diverse analogues of BZDs by adding N-H functionality (**R₂** in Figure 7.1) at the final step. Many bioactive 1,4-benzodiazepines include N-arylated BZDs and typical routes for preparing such N-H arylated molecules involve transition-metal catalysed couplings. These procedures often require high temperatures and have limited reaction scopes. Therefore, in Chapter 5, we described our approach to synthesise a small library of N-arylated 1,4-benzodiazepines by adopting a method of using unsymmetrical diaryliodonium salts with weak bases at room temperature. The method was also successfully applied to a similar 1,3,4-benzotriazepin-2-one derivative.

Finally, a scale-up synthesis of a BZD based potent BET-bromodomain inhibitor, **TC AC 28**, 6-(1*H*-Indol-4-yl)-8-methoxy-1-methyl-4H-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-4-acetic acid methyl ester, was conducted to enable the key chemical probe to be available for researchers. **TC AC 28** is a high affinity and highly selective BET bromodomain ligand with a binding efficiency of 40 nM and 800 nM towards BRd2(2) and Brd2(1) respectively. Our scale-up synthesis focussed on improving the last two steps of the original seven-step-protocol that were crucial to obtain near-gram quantities of the product. Changing the reagent quantities and the purification method significantly improved the problematic POCl₃ chlorination step. This enabled it

to be performed in one batch with 76% yield on about gram quantities of the final product. This penultimate step was originally performed in 12 small batches with a combined yield of 29%. The final Suzuki-Miyaura coupling step was significantly enhanced and was scalable to 0.8 g of product with 49% yield by modifying the reaction conditions and changing the base and the solvent.

Future studies of this work could involve addressing the drug-likeness of the library of C-H and N-H arylated 1,4-benzodiazepines by for example altering their lipophilicity. This could be achieved by exploring other types of C-H functionalisation methods, for instance by introducing heterocycles or by C-H amination etc.

Moreover, further diversification of the 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one could be explored by meta- and para- C-H activation (Figure 7.2).

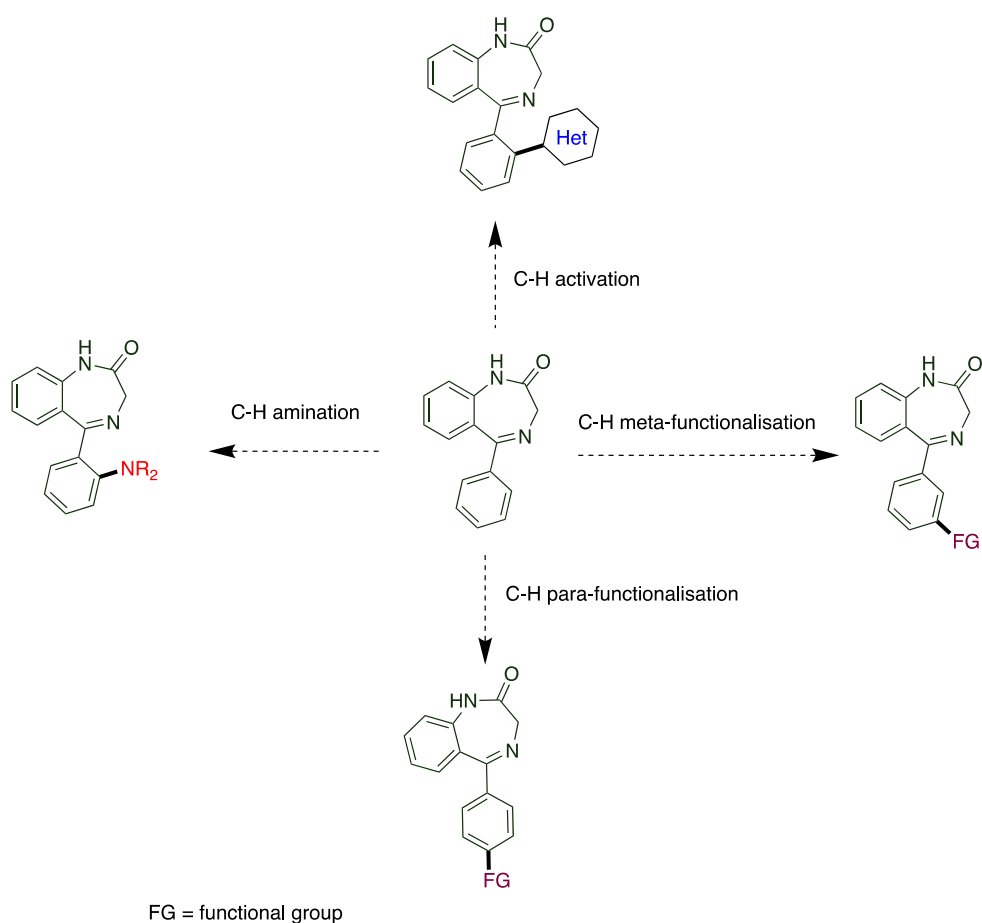


Figure 7.28: Strategies for further diversification of the 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one scaffold

The C-H functionalisation procedures described in Chapter 4.2 can be utilised to accomplish the diversification of the 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one scaffold.¹⁻¹⁸

7.2 Thesis Outcome

7.2.1 Publications

- R. Khan, R. Felix, P. D. Kemmitt, S. J. Coles, I. J. Day, G. J. Tizzard, and J. Spencer, *Advanced Synthesis and Catalysis*, **2016**, 358, 98-109.
- R. Khan, S. Boonseng, R. Felix, P. D. Kemmitt, S. J. Coles, G. J. Tizzard, G. Williams, O. Simmonds, J-L. Harvey, J. Attack, H. Cox, and J. Spencer, *Advanced Synthesis and Catalysis*, **2017**, 359, 3261-3269.
- R. Khan, G. Marsh, R. Felix, P. D. Kemmitt, M. G. J. Baud, A. Ciulli and J. Spencer, *ACS Omega*, **2017**, 2, 4328-4332.
- R. Khan, R. Felix, P. D. Kemmitt, S. J. Coles, G. J. Tizzard, and J. Spencer, *Synlett*, **2018**, 29, 193-198.

7.2.2 Awards and Honours

- First prize - PhD presentation, Annual Research Colloquium, University of Sussex, December 2017.

7.2.3 Presentations

- 'Late-stage C-H Functionalisation of Privileged Scaffolds: Synthesis of a library of Benzodiazepines' - Annual Research Colloquium, University of Sussex, September 2016. *Poster*.

- *Late-stage C-H Functionalisation of Privileged Scaffolds: Synthesis of a library of Benzodiazepines* – 23rd Lakeland Symposium on Heterocyclic Chemistry, Grasmere, May 2017. *Talk*.
- *Late-stage C-H Functionalisation of Privileged Scaffolds: Synthesis of a library of Benzodiazepines* – iCASE conference, AstraZeneca, Macclesfield, September 2017. *Talk*.
- *'Late-stage C-H Functionalisation of Privileged Scaffolds: Synthesis of a library of Benzodiazepines'* - Annual Research Colloquium, University of Sussex, December 2017. *Talk*.

7.2.4 Industrial placement

- 3 months industrial placement at Tocris Bioscience.
- Industrial scale-up synthesis and successful project delivery within tight timelines.
- Featured in Tocris's news-letter for the work conducted at the company.

7.2.5 Workshops

- RSC Medicinal Chemistry Residential School China, Shanghai Institute of Materia Medica, Shanghai, China, November 2014.

7.2.6 Media & Outreach

- Interviewed and featured in Worldwide Cancer Research blog for international women's day 2018. <https://www.worldwidecancerresearch.org/blog-post/drraysakhan/>
- Interviewed on local TV about the PhD research for Science Week 2017. <http://www.sussex.ac.uk/lifesci/chemistry/highlights/awards>

- Featured by a local magazine (Viva Brighton Magazine February 2018 issue #60)
- Speaker at Soapbox Science Brighton, 2018.

7.3 Reference

- 1 J. A. Leitch, C. L. McMullin, A. J. Paterson, M. F. Mahon, Y. Bhonoah and C. G. Frost, *Angew. Chemie - Int. Ed.*, 2017, **56**, 15131–15135.
- 2 C. Yuan, L. Zhu, R. Zeng, Y. Lan and Y. Zhao, *Angew. Chemie - Int. Ed.*, 2018, **57**, 1277–1281.
- 3 C. J. Teskey, A. Y. W. Lui and M. F. Greaney, *Angew. Chemie - Int. Ed.*, 2015, **54**, 11677–11680.
- 4 Q. Yu, L. Hu, Y. Wang, S. Zheng and J. Huang, *Angew. Chemie - Int. Ed.*, 2015, **54**, 15284–15288.
- 5 Z. Fan, J. Ni and A. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 8470–8475.
- 6 Z. Fan, J. Li, H. Lu, D. Y. Wang, C. Wang, M. Uchiyama and A. Zhang, *Org. Lett.*, 2017, **19**, 3199–3202.
- 7 B. Li, S. L. Fang, D. Y. Huang and B. F. Shi, *Org. Lett.*, 2017, **19**, 3950–3953.
- 8 C. C. Yuan, X. L. Chen, J. Y. Zhang and Y. S. Zhao, *Org. Chem. Front.*, 2017, **4**, 1867–1871.
- 9 O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298–19301.
- 10 N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877–5884.
- 11 C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2013, **15**, 3014–3017.
- 12 K.-H. Ng, Z. Zhou and W.-Y. Yu, *Chem. Commun.*, 2013, **49**, 7031.
- 13 C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2012, **14**, 656–659.
- 14 J. Kim, J. Kim and S. Chang, *Chem. - A Eur. J.*, 2013, **19**, 7328–7333.
- 15 M. Bhanuchandra, M. Ramu Yadav, R. K. Rit, M. Rao Kuram and A. K. Sahoo, *Chem. Commun.*, 2013, **49**, 5225.
- 16 M. R. Yadav, R. K. Rit and A. K. Sahoo, *Org. Lett.*, 2013, **15**, 1638–1641.
- 17 V. S. Thirunavukkarasu, K. Raghuvanshi and L. Ackermann, *Org. Lett.*, 2013, **15**,

3286–3289.

- 18 Y. Shin, S. Han, U. De, J. Park, S. Sharma, N. K. Mishra, E. K. Lee, Y. Lee, H. S. Kim and I. S. Kim, *J. Org. Chem.*, 2014, **79**, 9262–9271.